July 1979

American Heart Journal

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George E Burch *Editor*
James A Cronvich *Assistant Editor*
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INDICATIONS For the p ophyla s and long term t eatment of pat ents w th f equent or ecu e t a ginal pa n and reduced e erc se tole ance associated with a g na pec toris rather than for the t eatme t of the acute attack of ang na pecto s s ce its onset is somewhat slower than that of n troglycer n

PRECAUTIONS As with other effect e n t ites some fall in blood p ess e may occu w th large doses

Caut on should be observed n adm niste ng the d ug to pat ents w th a h story of e cent cerebral hemorrhage beca se of the vasod lat on wh ch occu s in the area Although therapy pe m ts mo e normal act vity the pat ent should not be allowed to m sinte p et freedom f om ang nal attacks as a sig al to d op all rest ict ons

SIDE EFFECTS No se ous side effects ha e been reported In sublingual therapy a tingl ng se sat on (l ke that of n t oglycer n) may somet mes be noted at the poi t of tablet contact w th the mucous memb ane If object o able this may be m t gated by placing the tablet in the buccal pouch As w th n t oglyce in o other effect ve n trates tempo ary vascula headache may occur du ing the f st few days of the apy Th s can be controlled by tempo ary dosage reduct on in orde to allow adjustments of the ce ebral hemodynam cs to the in t al ma ked ce ebral asod lat on These headaches usually d sappea w th n one week of cont nuous therapy but may be m m zed by the admin strat o of a algesics

M ld gastro ntest nal d sturba ces occu occas onally w th la ge doses and may be controlled by ed c g the dose tempo a ly

DOSAGE The py may be t ated w th 10 mg sublingually p io to each a tic pated physical or emot onal st ess a d at bedt me fo pat ents subject to octu nal attacks The dose may be eased o decreased as needed

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(erythrityl tetranitrat

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100 and 300 mg scored Tablets

- inhibits uric acid formation
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Zyloprim (allopurinol) is intended for

1 treatment of gout either primary or secondary to the hyperuricemia associated with blood dyscrasias and their therapy

2 *treatment of primary or secondary uric acid nephropathy with or without accompanying symptoms of gout*

3 *treatment of patients with recurrent uric acid stone formation*

4 *prophylactic treatment to prevent tissue urate deposition, renal calculi or uric acid nephropathy in patients* with leukemias, lymphomas and malignancies who are receiving cancer chemotherapy with its resultant elevating effect on serum uric acid levels

CONTRAINDICATIONS Use in children with the exception of those with hyperuricemia secondary to malignancy The drug should not be employed in nursing mothers

Patients who have developed a severe reaction to *Zyloprim should not be restarted on the drug*

WARNINGS ZYLOPRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION In some instances a skin rash may be followed by more severe hypersensitivity reactions such as exfoliative urticarial and purpuric lesions as well as Stevens Johnson syndrome (erythema multiforme) and *very rarely a generalized vasculitis which may lead to irreversible hepatotoxicity and death*

A few cases of reversible clinical hepatotoxicity have been noted and in some patients asymptomatic rises in serum alkaline phosphatase or serum transaminase have been observed Accordingly periodic liver function tests should be performed during the early stages of therapy particularly in patients with *pre-existing liver disease*

Patients should be alerted to the need for due precautions when engaging in activities where alertness is mandatory

Nevertheless iron salts should not be given simultaneously with *Zyloprim* This drug should not be *administered* to immediate relatives of patients with idiopathic hemochromatosis

In patients receiving Purinethol® (mercaptopurine) or Imuran® (azathioprine) the concomitant administration of 300-600 mg of Zyloprim per day will require a reduction in dose to approximately one-third to one-fourth of the usual dose of mercaptopurine or azathioprine Subsequent adjustment of doses of Purinethol or Imuran should be made on the basis of therapeutic response and any toxic effects

Usage in Pregnancy and Women of Childbearing Age Zyloprim® (allopurinol) *should be used in pregnant* women or women of childbearing age *only if the potential* benefits to the patient are weighed against the *possible* risk to the fetus

PRECAUTIONS Some investigators have reported an *increase in acute attacks of gout during the early stages* of allopurinol administration even when *normal or subnormal* serum uric acid levels have been attained

It has been reported that allopurinol prolongs the half life of the anticoagulant dicumarol This interaction should be kept in mind when allopurinol is given to patients already on anticoagulant therapy and the coagulation *time should be reassessed*

A fluid intake sufficient to yield a daily urinary output of at least 2 *liters and the maintenance of a neutral or,* preferably slightly alkaline urine are desirable to (1) avoid the theoretic possibility of formation of xanthine calculi under the influence of Zyloprim therapy and (2) help prevent renal precipitation of urates in patients receiving concomitant *uricosuric agents*

Patients with impaired renal function require less drug and should be carefully observed during the early stages *of Zyloprim administration and the drug withdrawn if* increased abnormalities in renal function appear

In patients with severely impaired renal function, or decreased urate clearance the half life of oxipurinol in the plasma is greatly prolonged Therefore a dose of 100 mg per day or 300 mg twice a week or perhaps less may be sufficient to maintain adequate xanthine oxidase *inhibition to reduce serum urate levels* Such patients should be treated with the lowest effective dose in order to minimize side effects

Mild reticulocytosis has appeared in some patients

As with all new agents periodic determination of liver and kidney function and complete blood counts should be performed especially during the first few months of therapy

ADVERSE REACTIONS

Dermatologic Because in some instances skin rash has been followed by severe hypersensitivity reactions it is recommended that therapy be discontinued at the first sign of rash or other adverse reaction (see WARNINGS). Skin rash usually maculopapular is the adverse reaction most commonly reported
Exfoliative urticarial and purpuric lesions Stevens *Johnson syndrome (erythema multiforme) and toxic* epidermal necrolysis have also been reported
A few cases of alopecia with and without accompanying dermatitis have been reported
In some patients with a rash restarting Zyloprim (allopurinol) therapy at lower doses has been accomplished without untoward incident

Gastrointestinal Nausea vomiting diarrhea, and intermittent abdominal pain have been reported

Vascular There have been rare instances of a generalized *hypersensitivity vasculitis or necrotizing angiitis* which have led to irreversible hepatotoxicity and death

Hematopoietic Agranulocytosis anemia aplastic anemia bone marrow depression leukopenia pancytopenia and thrombocytopenia have been *reported* in patients most of whom received concomitant drugs with potential for causing these reactions Zyloprim® *(allopurinol) has been neither implicated nor excluded as a cause of these reactions*

Neurologic There have been a few reports of peripheral *neuritis occurring while patients were taking Zyloprim Drowsiness has also been reported* in a few patients

Ophthalmic There have been a few reports of cataracts found in patients receiving Zyloprim It is not known if the cataracts predated the Zyloprim therapy Toxic cataracts were reported in one patient who also received an anti-inflammatory agent again the time of onset is unknown In a group of patients followed *by Gutman and Yü for up to five years on Zyloprim therapy no evidence of ophthalmologic effect attributable* to Zyloprim was reported

Drug Idiosyncrasy Symptoms suggestive of drug idiosyncrasy have been reported in a few patients This *was characterized by fever chills leukopenia or leukocytosis eosinophilia arthralgias skin rash pruritus nausea and vomiting*

OVERDOSAGE Massive overdosing or acute poisoning by Zyloprim has not been reported

HOW SUPPLIED 100 mg (white) scored tablets bottles of 100 and 1000 300 mg (peach) scored tablets bottles of 30 100 and 500 Unit dose packs for each strength also available

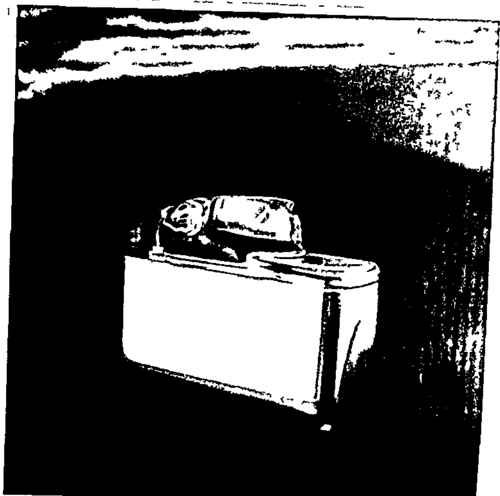
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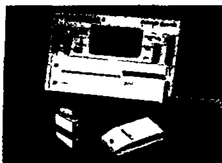


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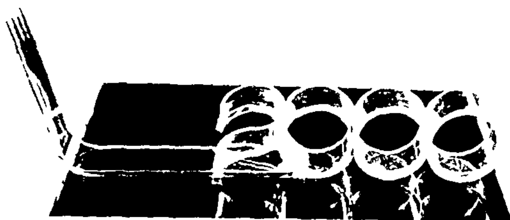
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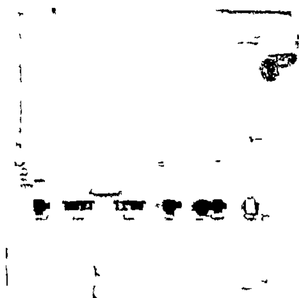
*Currently under investigational study

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INDICATIONS Fo the p ophyla is and long term t eatme t of patients with frequent or ecurrent anginal pa and reduced e e c se tole a ce associa ed with ang na pe to is rather than fo the t eatment of the ac te attack of ang na pecto is S nce its onset s somewhat slowe than that of t oglyce in

PRECAUTIONS As with o he e fect ve n t tes some fall in blood pressu e may occur w th large doses

Caution should be observed in adm iste ing the d ug to pa ents with a h story of e cent ce ebral hemo rhage because of the asod lation which occurs in the a ea Although the apy perm s mo e normal activ ty the pat e t should not be allowed to misin erp et f eedom f om ang nal attacks as a signal to d op all es ictions

SIDE EFFECTS No serious side e fects have bee epo ted In ublingual the apy a tingling sensation (ike that of troglyce in) may somet mes be oted at the point of tablet contact with the mucous memb a e If ob e tiona le th s may be mitiga ed by placing the tablet in the buccal pouch As w th oglyce n o othe effective t a es temporary ascula heada he may occ du ing the f st few days of the apy This can be controlled by temporary dosa e edu tion in o de to allow ad ustments of the ce eb al hemodynam cs to the init al marked ce eb al asod lation These headaches usually disappea within one week of continuous the apy but may be m nim zed by the adminis a ion of a alge sics

M ld gastro es inal disturbances occu occasionally with la e doses and may be con rolled by educing the dose tempora y

DOSAGE The a y may be initia ed with 10 mg s b in ally p io to ea h a cipa ed physical or emotional s ess and at bed me fo pa ents subject to nocturnal a acks *The dose may be inc eased or de eased as eeded*

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PRECAUTIONS As with other effective nitrites some fall in blood pressure may occur with large doses

Caution should be observed in administering the drug to patients with a history of recent cerebral hemorrhage because of the vasodilation which occurs in the area. Although therapy permits more normal activity the patient should not be allowed to misinterpret freedom from anginal attacks as a signal to drop all restrictions

SIDE EFFECTS No serious side effects have been reported In sublingual therapy a tingling sensation (like that of nitroglycerin) may sometimes be noted at the point of tablet contact with the mucous membrane If objectionable this may be mitigated by placing the tablet in the buccal pouch As with nitroglycerin or other effective nitrates temporary vascular headache may occur during the first few days of therapy This can be controlled by temporary dosage reduction in order to allow adjustments of the cerebral hemodynamics to the initial marked cerebral vasodilation These headaches usually disappear within one week of continuous therapy but may be minimized by the administration of analgesics

Mild gastrointestinal disturbances occur occasionally with larger doses and may be controlled by reducing the dose temporarily

DOSAGE Therapy may be initiated with 10 mg sublingually prior to each anticipated physical or emotional stress and at bedtime for patients subject to nocturnal attacks The dose may be increased or decreased as needed

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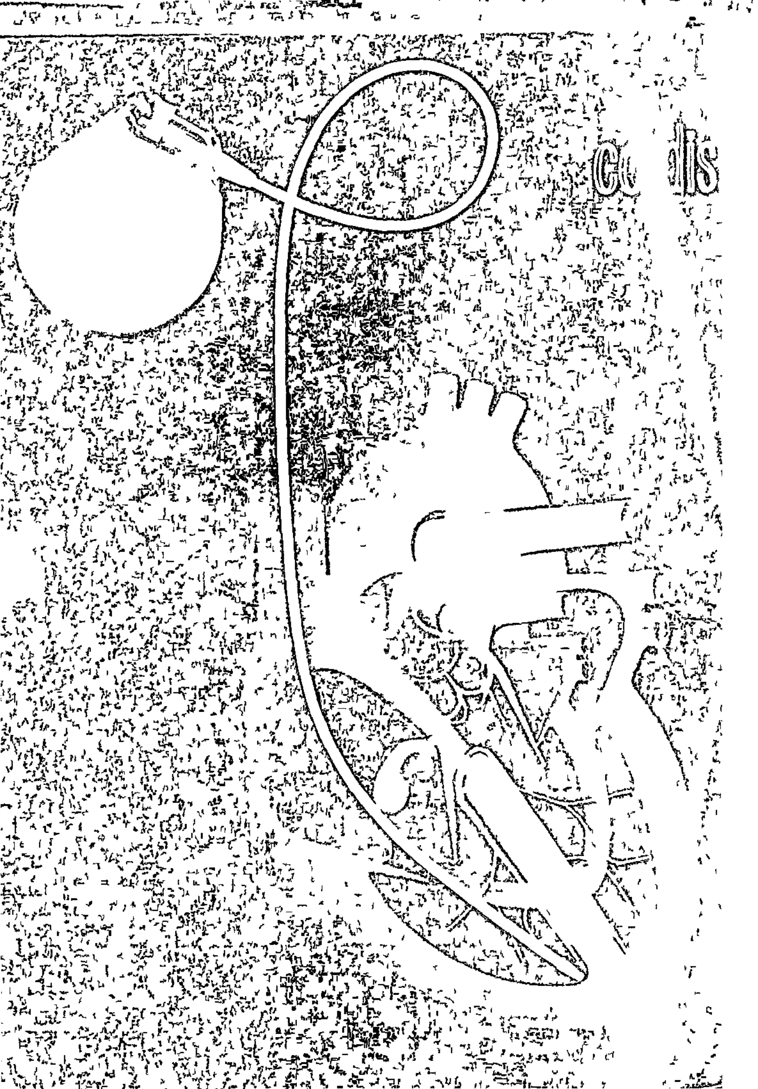
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American Heart Journal

July 1979 Volume 98 Number 1

Editorial

Management of the asymptomatic carotid bruit

William S Fields M D
Houston Texas

The management of the patient in whom an asymptomatic carotid bruit is encountered is still a subject of considerable controversy It is clear however that every effort must be made to determine that the abnormal sound is well localized to the midcervical region just behind and below the angle of the mandible and that it either disappears or diminishes in intensity as one moves the stethoscope lower in the neck A bruit is more likely to become audible when narrowing in the artery reaches 50 per cent of the cross sectional diameter but the sound may disappear when the narrowing exceeds 85 per cent to 90 per cent The over all correlation between bruits and demonstrable carotid arterial occlusive disease is about 60 per cent There is certainly no question that a carotid bruit detected in a patient with symptoms related to the ipsilateral eye or cerebral hemisphere is a significant clinical finding It is only when there are no such symptoms that a controversy may arise regarding the clinical significance of the bruit

The majority of patients in whom an asymptomatic bruit is encountered are those who are being examined for life insurance or having a routine annual or semiannual checkup Such persons usually are in otherwise good health even from the cardiovascular standpoint except perhaps for a mild to moderate degree of hypertension When thorough probing for a history of symptoms suggestive of cerebral ischemia is unrevealing the immediate question facing the physician is whether to recommend further diagnostic tests If one decides to evaluate the patient further discretion dictates that noninvasive methods for determining carotid artery pressure and flow should first be performed If no evidence of arterial obstruction is found then treatment if any may be confined to the administration of antiplatelet agents especially aspirin and plans should be made to repeat the tests in six to eight months

The real dilemma arises however when the noninvasive test results suggest the presence of stenosis in the cervical portion of the carotid artery and a decision must be made regarding arteriography which even in the most experienced hands carries an element of risk. Perhaps the best body of data available to assist the physician in making this decision may be found in the study of patients with bilateral carotid stenosis and unilateral symptoms Arterial reconstructive surgery is usually carried out on the artery of the symptomatic side although arteriographically that artery may not be the one with the greatest degree of narrowing Following unilateral arterial repair the patient is left with narrowing in the artery of the asymptomatic side—a situation comparable to that in an asymptomatic individual with a unilateral bruit Many surgeons and some physicians would state without reservation that the remaining lesion constitutes a threat

From the Department of Neurology Medical School, University of Texas Health Science Center at Houston.

Received for publication May 30 19 8

Reprint requests William S Fields M.D Dept of Neurology Medical School University of Texas Health Science Center at Houston P O Box 20708 Houston Texas 7 0.5

to the patient and therefore operation on the second side should be performed promptly Unfortunately there is no conclusive evidence to support the contention that such a lesion is necessarily a prestroke' lesion and to fail to repair it would constitute a breach of good medical practice In one reported series, 250 patients who had bilateral carotid stenosis of more than 50 per cent and in whom surgery was performed on the symptomatic side only were followed for a minimum period of two years No further strokes occurred during the follow up and a second operation was performed in only two patients who became symptomatic after the first operation

A highly experienced vascular surgeon who has performed well over 1 000 carotid operations reported 149 endarterectomies in 114 patients categorized by him as having symptomatic carotid bruits In this series he had no operative mortality but two patients sustained permanent neurologic deficits During the long term follow up none of the patients suffered fatal cerebral infarcts but one had a major stroke and another a moderately severe one As a control series this surgeon used 102 of his patients who were not operated upon for a variety of reasons During the 10 year follow up period 28 patients of this group experienced transient ischemic attacks and were operated on and 48 had cerebral infarcts from two days to four years after detection of the bruit In his summary he states If hazardous lesions are demonstrated carotid endarterectomies may be recommended for selected patients without multiple risk factors to prevent the occurrence of ischemic cerebral episodes Unfortunately, there are no data nor is there any test which enables us to state unequivocally which patient has a hazardous lesion

For a long time I have held the opinion that carotid operations should be done only by experienced surgeons who have demonstrated the ability to perform these procedures and to maintain their total serious morbidity and mortality rate at 1 per cent or less This position most assuredly applies when one is considering recommending an operation on an asymptomatic patient

In the past 12 months two large cooperative studies, one in the United States and the other in Canada have both showed that aspirin used as an antiplatelet agent will prevent transient ischemic attacks in a statistically significant proportion of patients suffering from transient cerebral ischemia In view of this I feel that it would be far better when one considers the risks of surgery to treat patients in whom asymptomatic bruits are encountered with 650 mg of aspirin twice daily after meals It is necessary of course to eliminate from such medical management persons who have a blood dyscrasia active peptic ulcer or a specific idiosyncracy to aspirin

Perhaps a controlled study of asymptomatic patients with carotid bruits randomly allocated to surgical or nonsurgical management would provide the information necessary to enable a physician to arrive at an appropriate decision when confronted with the need to make a choice

Clinical communications

Conduction defects in aortic valve disease

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The association of conduction defects and aortic valve disease is well documented and was first described by Yater and Cornell in 1935[1] The production of conduction defects is a recognized hazard following aortic valve replacement and other surgical procedures where the operative field is in the vicinity of the major conducting pathways[2,3] There have been isolated reports of reversal of surgically induced and non surgical complete heart block following aortic valve replacement in patients with aortic stenosis[4] The true incidence etiology and influence of conduction defects on prognosis in patients with aortic valve disease has however received little attention The purpose of this paper is to analyze the electrocardiogram in a number of patients before and after homograft replacement of the aortic valve in an attempt to answer some of these questions

Materials and methods

Serial electrocardiograms of 426 consecutive patients undergoing homograft replacement of the aortic valve between September 1969 and June 1976 were analyzed with respect to the presence or absence of conduction defects Patients undergoing additional procedures to the mitral or other valves were excluded A further three patients who died at the time of operation were also excluded

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Electrocardiograms were recorded preoperatively then daily for the first 8 days after operation at 2 months postoperatively and thereafter at six monthly intervals. The study group comprised 310 males and 116 females with an age range between 8 years and 72 years (mean 55 years) At the time of operation 271 patients (64 per cent) were in Functional Class III or IV of the New York Heart Association (N Y H A.) classification One hundred thirty seven patients (32 per cent) were in Class II and 18 patients (4 per cent) were in Class I The dominant lesion was aortic stenosis in 249 patients and aortic regurgitation in 177 patients

All patients underwent right and left heart catheterization prior to aortic valve replacement. Coronary angiography which only became a routine procedure in patients with aortic valve disease in this center from 1974 onwards was performed in 179 patients by the methods described by Sones or Judkins All patients underwent homograft replacement of the aortic valve using a fresh unstented antibiotic sterilized homograft using two suture lines and coronary perfusion at 30° C[7,8] Isolated valve replacement was performed in 332 patients (78 per cent) Additional aortocoronary bypass grafting was performed in 26 patients (6 1 per cent) and replacement of the ascending aorta with a Dacron prosthesis was done in a further 26 patients (6 1 per cent) Replacement of the aortic root with reimplantation of the coronary arteries into the homograft valve was performed in 16 patients (3.8 per cent)[9] Other procedures included sub valvar myectomy in six patients (1 4 per cent) sub valvar myotomy in 10 patients (2 3 per cent) and insertion of a permanent epicardial pacing system

Table I Distribution of preoperative conduction defects in patients with aortic valve disease

Conduction defect	Aortic stenosis N = 69		Aortic regurg N = 43	
	No	%	No	%
Left anterior hemiblock	29	42%	21	49%
L B B B	14	20%	5	12%
R B B B	3	4%	1	2%
Trifascicular block	5	7%	0	0%
1° A V block	13	19%	24	33%
Complete A V block	5	7%	2	5%

in eight patients (1 9 per cent) Following operation, 79 patients were subsequently reinvestigated by repeat cardiac catheterization and coronary angiography subject to informed consent at times varying between 3 to 84 months (mean 40 months)

In an attempt to define more precisely the etiology of conduction defects the following parameters were analyzed (1) presence and distribution of valvular calcification (2) left ventricular function and (3) coronary artery disease Evidence of valvular calcification extending into the ventricular septum was recorded at the time of operation An ejection fraction of less than 0 45 and/or a cardiac index of less than 2 0 liters/M²/min was taken as evidence of impaired left ventricular function Significant coronary artery disease was defined as a 50 per cent or more narrowing in a major coronary vessel Left anterior hemiblock was defined by criteria previously described by Rosenbaum [10]

Follow up data was available in all patients who routinely attend this hospital at annual intervals

Results

Preoperative conduction defects Preoperative conduction defects were present in 69 patients (28 per cent) with aortic stenosis and in 43 patients (24 per cent) with aortic regurgitation (Table I) Abnormalities of conduction in the left bundle branch were common in both groups, and accounted for approximately two thirds of preoperative conduction defects Abnormalities of atrioventricular conduction particularly first degree A V block were responsible for most of the remainder in both groups In patients with aortic stenosis extensive calcification in the

Table II Etiology of preoperative conduction defects in patients with aortic valve disease

Etiology of conduction defect	Aortic stenosis N = 69		Aortic regurg N = 43	
	No	%	No	%
Ventricular septal calcification	40	58%	6	14%
Poor left ventricular function	17	25%	27	63%
Coronary artery disease	10	14%	6	14%
Ventricular septal abscess	2	3%	4	9%

Table III Influence of homograft replacement of the aortic valve on preoperative conduction defects

Changes in conduction defects following A V R	Aortic stenosis N = 69		Aortic regurgitation N = 43	
	No	%	No	%
Unchanged	47	68%	28	65%
Reversal	15	22%	10	3%
Progression	7	10%	[illegible]	12%

ventricular septum was reported in 40 (58 per cent) of the 69 patients (Table II) This was occasionally evident radiographically (Fig 1) In comparison the incidence of septal calcification in patients with normal pre and postoperative conduction was only 12 per cent Poor left ventricular function was present in 17 patients (25 per cent) However in half these patients and particularly those with abnormalities of conduction in the left bundle branch additional septal calcification was reported

In patients with aortic regurgitation, conduction defects were associated with poor left ventricular function in 27 (63 per cent) (Table II) Significant coronary artery disease was present in six patients (14 per cent) and ventricular septal calcification in a further six patients (14 per cent) Conduction defects were associated with the development of an acute ventricular septal abscess in four patients (9 per cent)

In the majority of patients preoperative conduction defects were not influenced by operation Thus the electrocardiogram remained unchanged following valve replacement in 47 (68

Table IV Progression and reversal of preoperative conduction defects following aortic valve replacement in relation to type of conduction abnormality

Conduction defect	Aortic stenosis		Aortic regurg	
	No rev	%	No rev	%
Left anterior hemiblock	7/28	25%	1/17	6%
1 A V block	7/11	64%	7/12	58%
Complete A V block	1/ 5	20%	2/ 2	100%
LBBB RBBB Trifascicular block	None reversed		None reversed	

Table V Reversal of preoperative conduction defects following aortic valve replacement in relation to etiology of conduction abnormality

	Aortic stenosis		Aortic regurgitation	
	No reversed	%	No reversed	%
Poor left ventricular function	6/17	35%	5/27	19%
Ventricular septal abscess	2/2	100%	3/4	75%
Coronary artery disease	2/10	20%	1/6	17%
Ventricular septal calcification	5/40	13%	1/6	17%



Fig 1 Left lateral chest x ray of a patient with severe aortic stenosis showing extensive aortic valve calcification extending into the ventricular septum (*arrow*) This patient showed wide variations in conduction between isolated RBBB isolated LBBB and *trifascicular block*.

per cent) out of 69 patients with aortic stenosis and conduction defects and in 28 (65 per cent) of 43 patients with aortic regurgitation (Table III) Normal conduction was restored in 15 patients (22 per cent) with aortic stenosis and in 10 patients (23 per cent) with aortic regurgitation Reversal of conduction abnormalities were restricted in the main to patients with first degree A V block or LAH (Table IV) However normal conduction was restored in three patients who had shown complete heart block The initial lesion was aortic regurgitation in two and aortic stenosis in one Reversal *of first degree A V block* occurred in seven out of 11 patients (64 per cent) with aortic stenosis and in seven out of 12 patients (58 per cent) with aortic regurgitation LAH was reversed in seven out of 28 patients (25 per cent) with aortic stenosis and progressed to complete LBBB in four patients (14 per cent) In contrast LAH was reversed in only one of 17 patients (6 per cent) with aortic regurgitation and progressed to LBBB in five patients (29 per cent) Progression of conduction defects occurred in a further three patients with aortic stenosis Two patients with RBBB developed trifascicular block and one patient with first degree A V block developed complete *heart block* *Progression* of conduction defects occurred in five patients (12 per cent) with aortic regurgitation and in each case L A H progressed to LBBB Improvement in conduction did not occur in any patient with LBBB or RBBB

In patients with aortic stenosis, reversal of preoperative conduction abnormalities occurred within three months of valve replacement in five patients (31 per cent) and at a time between 12 months and 36 months (mean 17 months) in the remaining 11 patients In patients with aortic

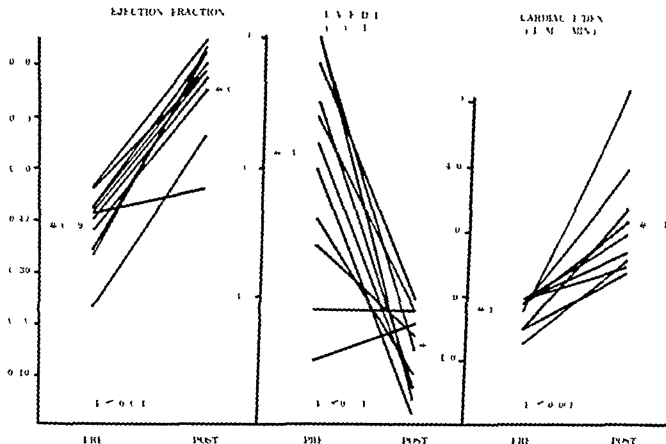


Fig 2 Changes in ejection fraction, LVEDP and cardiac index in 11 patients following homograft replacement of the aortic valve in whom preoperative conduction defects were reversed

regurgitation reversal within the first 3 months following surgery was seen in only one patient (10 per cent) and at a time varying between 4 months and 27 months (mean 14 months) in the remaining nine patients Progression of conduction defects within the first three months following valve replacement was observed in two patients (17 per cent) both with aortic stenosis Progression of conduction abnormalities occurred in a further 10 patients at a time varying between 16 months and 78 months (mean 43 months)

In 11 out of the 25 patients (44 per cent) showing reversal of conduction defects postoperatively, the initial abnormality was associated with poor left ventricular function (Table V) At subsequent re-investigation hemodynamic parameters including ejection fraction cardiac index and L.V E D P returned to normal (Fig 2) In contrast in the six patients with poor left ventricular function showing progression of conduction defects after operation there was over all deterioration in left ventricular performance (Fig 3) Reversal of conduction defects occurred in three patients with coronary artery disease following combined valve replacement and coronary artery bypass grafting and in a further three patients following surgical treatment of a ventricular septal abscess

There were 15 deaths (5 4 per cent) within the first month of operation and 13 late deaths (4 7 per cent) in 275 patients with normal conduction throughout the pre and postoperative period In the group of 69 patients with aortic stenosis there were three early deaths (4 4 per cent) and 11 late deaths (15 9 per cent) Extensive coronary artery disease was present in all three patients who died in the early postoperative period Two of these patients had shown bifascicular block and the third LBBB with left axis deviation Of the 11 late deaths four occurred in patients with LBBB and in all these cases there was associated left axis deviation Four further deaths were associated with LAH and in three of these the defect progressed to LBBB with left axis deviation Of the remaining three deaths two were associated with RBBB and one with complete heart block despite satisfactory pacemaker function In the group of 43 patients with aortic regurgitation

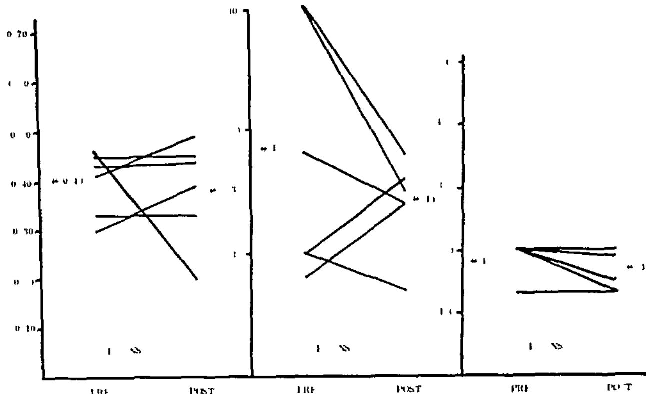


Fig 3 Changes in ejection fraction LVEDP and cardiac index in six patients showing progression of preoperative conduction defects following homograft replacement of the aortic valve

there were four early deaths (9 3 per cent) and four late deaths (9 3 per cent) All four late deaths were associated with progression of LAH to LBBB with left axis deviation Despite a good initial clinical result progressive deterioration with increase in heart size and the development of left ventricular failure occurred in all these four patients despite satisfactory valve function Significant coronary artery disease was present in only two of these patients at postmortem examination Throughout both groups there were no deaths in patients who either preoperatively had LBBB with normal QRS axis or who subsequently developed this combination

Postoperative conduction defects Conduction defects appeared for the first time following valve replacement in 39 patients This incidence represents 5 3 per cent of those undergoing operation with no evidence of a previous conduction abnormality In this group there were two early deaths (5 1 per cent) and four late deaths (10 3 per cent) In 19 patients 12 with aortic stenosis and seven with aortic regurgitation the conduction defect developed within the first 4 weeks of operation Conduction disturbances during this period were closely related to surgical procedure Attempted clearance of calcium from the ventricular septum was associated with the development of conduction abnormalities in 12 patients and included LAH in six patients LBBB in three RBBB in two and complete heart block in one Four cases of LAH followed subvalvar myotomy Evacuation of a ventricular septal abscess produced LBBB in one patient and complete heart block in another Failure to perfuse a small right coronary artery was associated with the development of RBBB in one patient The two early deaths in this group occurred in the two patients developing complete heart block

Fresh conduction defects appeared in 20 patients at times varying between 14 and 48 months following operation Failure of the homograft valve with subsequent deterioration in left ventricular function was associated with the development of LAH in five patients with additional first degree A V block in one patient Four of these patients subsequently died In the remaining 15 patients no apparent cause could be

determined These patients remained symptom free with good homograft function

Discussion

Conduction defects are common in patients with aortic valve disease and in the present series were found in approximately one quarter of all patients coming to valve replacement The over all incidence was similar in patients with aortic stenosis to those with aortic regurgitation The incidence of atrioventricular conduction disturbances was significantly higher in patients with aortic regurgitation whereas abnormalities distal to the bundle of His were more frequent in patients with aortic stenosis These findings are confirmed by Friedman and associates[1] who in a series of 25 patients with aortic valve disease undergoing His bundle electrocardiography found that A H intervals were significantly longer in patients with aortic regurgitation compared to those with aortic stenosis while H V intervals were longer in patients with aortic stenosis

The high incidence of conduction defects in patients with aortic stenosis and heavy calcification of the aortic valve may be related to the close anatomical juxtaposition of the aortic valve and the left bundle system Migration of calcium into the ventricular system was a frequent finding at operation in these patients and was associated with a high incidence of conduction defects involving the left bundle branches In contrast the incidence of septal calcification in patients with aortic regurgitation was low and did not differ significantly from that found in patients with normal conduction

In patients with aortic regurgitation conduction defects were often associated with poor left ventricular function This association might possibly be the result of tension on or deformity of conducting tissue in patients with a large left ventricular cavity and as such would be expected to occur more frequently in the volume overloaded ventricle It is unlikely that the presence of conduction defects per se could result in the development of such a degree of left ventricular dysfunction[1] We have frequently observed the reversal of conduction defects in patients with large poorly contracting left ventricles at the time of initiation of cardiopulmonary bypass only to see the defect return when bypass is discontinued

Histological studies have shown that interstitial fibrosis involving the conducting tissue, with the subsequent production of conduction abnormalities may occur in the chronically dilated left ventricle from a variety of causes[13] Since the fibrotic changes so produced are unlikely to be reversible conduction abnormalities resulting *from such a mechanism are likely* to be permanent despite reduction in left ventricular volume following valve replacement This may in part explain the failure of reversal of some conduction defects following operation particularly in patients with aortic regurgitation in whom left anterior hemiblock was reversed in only one patient

Significant coronary artery disease was found in association with conduction defects in only a minority of patients and the incidence was similar in patients with aortic stenosis and aortic regurgitation

The early mortality following valve replacement was not significantly higher in patients with *preoperative conduction defects regardless of the* initial haemodynamic lesion In particular, there was no increase in early mortality in patients with left bundle branch block There was however a significant increase in late mortality in patients with preoperative conduction defects particularly in patients with aortic stenosis Of the total number of 15 late deaths in patients with preoperative conduction defects 11 (73 per cent) occurred in association with the combination of left bundle branch block and left axis deviation The poor prognosis of patients with additional left axis deviation has been commented on previously[14] In contrast to other reports[15, 16] the incidence of coronary artery disease in this group was not significantly higher than in other patients Lewis and co workers[17] and Haft and colleagues[18] also reported a relatively low incidence of coronary artery disease in patients with left bundle branch block Our findings support the view that this combination may reflect more widespread and diffuse myocardial damage[19] This is suggested by the high incidence of left ventricular failure in this group in the late postoperative period despite satisfactory homograft valve function In contrast left bundle branch block with a normal axis was not associated with an increased late mortality rate This may be the result of more localized damage to the conducting tissue particularly in patients with

aortic stenosis and extensive valvular calcification

Reversal of preoperative conduction defects after operation occurred exclusively in patients with left anterior hemiblock or atrioventricular abnormalities including three patients with complete heart block Reversal of atrioventricular defects occurred in over 50 per cent of patients regardless of the initial hemodynamic lesion whereas reversal of left anterior hemiblock was seen more frequently in patients with aortic stenosis In the majority of patients reversal occurred in those with poor preoperative left ventricular function and who subsequently showed evidence of improved left ventricular function after operation In contrast progression of conduction defects was usually associated with deterioration of left ventricular function The mechanism of such changes remains uncertain Decalcification of the ventricular septum is unlikely to be responsible (vide infra) Similarly conduction defects produced by fibrosis involving the conducting tissue are unlikely to reverse Changes in left ventricular geometry with reduction in ventricular volume and wall stress may reduce tensile forces and distortion acting on the conducting tissue in the absence of fibrosis and facilitate the return to normal conduction

Complete heart block is well documented in patients with infective endocarditis and may occur as a result of formation of a ventricular septal abscess Urgent valve replacement with surgical treatment of the abscess resulted in restoration of normal conduction in five out of six patients in the present series Conduction defects in patients with coronary artery disease were also reversed in a small proportion of cases following successful coronary artery bypass grafting

Fresh conduction defects occurred following valve replacement with an over all incidence of 5 3 per cent Of 19 patients developing conduction defects within the first four weeks of operation 14 (74 per cent) involved the left bundle or its branches Conduction defects occurring during the early postoperative period were with one exception all associated with additional surgical procedures particularly with attempts to clear calcium from the ventricular septum subvalvar myectomy or subvalvar myotomy Since such procedures were usually performed in patients with aortic stenosis this incidence of conduction abnormalities was higher in this group compared to patients with aortic regurgitation

Follath and Ginks reported the appearance of fresh conduction defects in 12 (29 per cent) out of 42 patients following the insertion of a ball valve prosthesis The significantly higher incidence in this group of patients compared to the present series using homograft valves may be related to the presence of a rigid stent causing pressure on surrounding structures together with the seating of the valve in a position in closer proximity to the conducting tissue

Although conduction defects occurring in the late postoperative period were associated with failure of the homograft valve in some patients and subsequent development of left ventricular failure nevertheless in most patients no apparent cause was evident These patients continue to remain symptom free with good valve function It is possible that fibrosis extending from the suture lines may interfere with conduction in such patients

The appearance of fresh conduction defects following operation was not associated with a significant increase in either early or late mortality over all although in the subgroup of patients with valve failure there was a high mortality rate

Summary

Serial electrocardiograms of 426 patients undergoing homograft replacement of the aortic valve were analyzed with respect to the presence or absence of conduction defects (CD) in an attempt to define more precisely their etiology and relationship to prognosis The dominant lesion was aortic stenosis in 249 patients and aortic regurgitation in 177 patients *Preoperative* CD were present in 69 patients (28 per cent) with aortic stenosis and in 43 patients (24 per cent) *with aortic regurgitation* In those with aortic stenosis calcification in the ventricular septum or impaired left ventricular function were common and could have been important etiological factors In those with aortic regurgitation impaired left ventricular function was the dominant feature Coronary artery disease was present in a minority of patients in both groups In patients with aortic stenosis there were three early deaths (4 4 per cent) and 11 late deaths (15.9 per cent) In those with aortic regurgitation there were four early deaths (9 3 per cent) and four late deaths (9 3 per cent) Of 275 patients with normal

conduction throughout the pre and postoperative period there were 15 early deaths (5 4 per cent) and 13 late deaths (4 7 per cent) (Follow up 3 to 84 months Mean 36 months) Reversal of CD following operation occurred in more than half of those patients with first degree A V block regardless of the initial hemodynamic lesion and was associated with improvement in left ventricular function Reversal of left anterior hemiblock (LAH) occurred in approximately 30 per cent of cases Progression of LAH and the combination of left axis deviation with left bundle block (LBBB) were associated with a poor prognosis Fresh CD following operation occurred in 19 patients within 1 month of surgery and in 20 patients beyond this period of time In this group there were two early deaths (5 1 per cent) and four late deaths (10 3 per cent) Of 20 patients developing late conduction defects six were associated with valve failure and the development of poor left ventricular function In the remainder no apparent cause could be determined and this group may represent fibrosis occurring in the region of the conducting pathways

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Persistent ST segment elevation in left ventricular aneurysm before and after surgery

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After recovery from myocardial infarction persistent ST segment elevation in leads exhibiting abnormal Q waves is a sign suggesting the formation of a left ventricular aneurysm Although surgical resection of aneurysm is a widely employed and usually successful treatment leading to improved ventricular function and relief of disabling symptoms it remains unclear as to whether or not the postoperative clinical condition has an electrocardiographic expression in ST changes That is does a decline or normalization of ST segments parallel the improved clinical state? To examine this question standard 12 lead electrocardiograms were analyzed for ST segment changes before and after surgery and were correlated with changes of heart size seen on x ray and with NYHA Functional Class

Subjects and methods

Selection of patients for this study was based on survival for at least three months following resection of post myocardial infarction aneurysm of the left ventricle There were 74 patients of whom 53 were male with an age range of 32 to 65 years (mean 49 1 years) and 21 females whose ages ranged from 33 to 75 years (mean 53 4 years) According to the criteria of the NYHA functional classification prior to surgery 23 patients were judged to be in Class IV 39 in Class III 12 in Class II and none were Class I The principal symptoms were shortness of breath 61 patients chest pain 52 and palpitations seven Patients with small aneurysms and those who were asymptomatic or only mildly symptomatic were not selected for surgical treatment The postoperative follow up period ranged from 3 months to 52 months (mean 18.2 months)

Sixty patients (81 per cent) concurrently underwent aortocoronary artery bypass surgery with one to four saphenous vein jump grafts Thirty patients underwent a single bypass graft 24 had double grafts five had triple grafts and one had quadruple jump grafts Of the 30 with single artery bypasses 22 were to the left anterior descending coronary artery

A total of 266 electrocardiograms were analyzed averaging 3 6 per patient These included one tracing obtained within 2 days prior to surgery and several (two to five per patient) obtained following surgery No postoperative ECG s were included until at least 3 months had elapsed in order to avoid the inclusion of transient ST abnormalities that could have been attributed to operative trauma or pericarditis and in order to allow sufficient time to assess follow up status Electrocardiographic changes which excluded patients from this study included left bundle branch block left ventricular hypertrophy and QRS evidence of intraoperative or postoperative myocardial infarction Because there were few cases of inferior or posterior aneurysm encountered in this survey only anteri or apical and lateral aneurysms—those locations which could be reflected in Leads V_1 to V_6—were included in this analysis The electrocardiograms of the 74 patients were analyzed independently without knowledge of the NYHA Class or x ray findings ST segment elevations were measured

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Table I Evaluation subsequent to left ventricular aneurysm surgery

		Preoperative	Postoperative	
Functional Class (NYHA)				
Class I		0	39	
Class II		12	25	
Class III		39	8	
Class IV		23	2	
				P value
X ray				
Heart transverse diameter	mean	15 76 cm	15 09 cm	< 0 005
	SD	1 84	1 77	
	SEM	0 21	0 20	
Cardio thoracic ratio	mean	0 507	0 484	< 0 005
	SD	0 066	0 055	
	SEM	0 008	0 006	
ST segment elevation				
ΣST	mean	5 27 mm	4 71	< 0 025
	SD	2 74	2 71	
	SEM	0 32	0 31	
Single lead	mean	1 96	1 88	> 0 1
	SD	0 84	0 81	
	SEM	0 096	0 094	

Abbreviations SD = standard deviation SEM = standard error of the mean

Table II Postoperative ST segment elevation

	Improved	Unchanged	Worse
X ray parameters			
Improved	17	23	6
Unchanged	2	17	1
Worse	0	5	3
Functional Class (NYHA)			
Improved	16	40	10
Unchanged	3	5	0

with the aid of a hand lens to the nearest 0 5 mm at 80 msec from the J point ST elevations in the precordial leads of each ECG were expressed as (1) the sum of ST elevations of all affected leads (ΣST) and (2) the largest magnitude of ST elevations in a single lead for each tracing A postoperative ECG was considered unchanged if ΣST elevations or ST of a single lead was similar to the preoperative tracing within 2 mm The arbitrary definition of improvement was a decrease of ST elevation of more than 2 mm or a complete loss of ST elevations those with increased ST elevations exceeding 2 mm were considered electrocardiographically worse No attempt was made to assess qualitative changes in ST segment contours The data were analyzed using the paired Student t test

Standard chest x rays were examined, the PA films obtained immediately prior to operation were compared to the last available postoperative film Measurements were made of the transverse dimension (sum of mid right and mid left diameters) of the heart and the cardiothoracic (C/T) ratios were determined Heart size was considered improved when the postoperative film demonstrated a reduction of over all heart size of 1 cm or more

Results

Persistent elevation of the ST segments was present in all patients preoperatively and in no instance did ST return to the baseline in all affected leads after surgery nor were new ST segment depressions seen The mean ΣST was 5 27 preoperatively (range 14 0 to 0 5 mm) and 4 71 (range 19 5 to 0 5 mm) in the last postoperatively tracing (Table I) The postoperative reduction of the mean ΣST was statistically significant ($P < 0\ 025$) For the greatest elevation in a single lead the values were preoperatively mean 1 9 mm (range 5 0 to 0 5 mm) and 1 88 mm postoperatively the difference lacking significance ($P > 0\ 1$) As compared to the tracings prior to surgery 45 (60 8 per cent) electrocardiograms were unchanged 19 (25 7 per cent) were improved and 10 (13 5 per cent) were worse after aneurysmectomy (Table II)

Sixty six (89 2 per cent) patients improved their NYHA functional class after surgery eight were unchanged Symptoms remaining though generally less intense included 17 with chest pain 18 with shortness of breath and five had palpitations In the postoperative ECG s of the functionally improved patients the ST segments were unchanged in 40 (60 6%) worse in 10 (15 1 per cent) and improved in only 16 (24 2 per cent)

In evaluating the heart size by chest x rays prior to operation 13 (20 3 per cent) were considered normal Thirty six (48 7 per cent) had cardiothoracic ratios exceeding 0 5 Postoperative improvement of x ray features was highly significant ($P < 0\ 005$) for reduction of both heart size and C/T ratio Heart size was improved in 46 (62 2 per cent) patients unchanged in 20 and increased in eight patients following surgery

Of the 46 patients with x ray evidence of post operative improvement 17 (36 9 per cent) exhibited improvement of ST segments 23 were unchanged and six had higher elevation of the ST segment In the 19 cases whose ST segments were improved (less elevated) the heart size was also improved 17 (89 4 per cent) and clinical improvement was seen in 16 (84 2 per cent)

Discussion

The electrocardiogram often provides valuable clues to the presence of ventricular aneurysm and this has been recognized for many years The unusually high prevalence of abnormal ST displacements in the preoperative ECG of this study may be related to the method of selection of patients That is only symptomatic patients with clinically significant aneurysms underwent surgery thus patients with small aneurysms and who would be less likely to display ST changes were not operated Moreover the degree of ST elevation was only 0 5 mm in three of the subjects so that this degree of displacement could have been easily missed or considered unimportant on casual inspection of the electrocardiogram

The electrophysiological phenomenon of persistent ST elevations in patients with ventricular aneurysm either before or after surgery remains unexplained It has been suggested that the injury current could be due to chronic ischemia or traction of viable myocardial fibers adjacent to the aneurysm or those interspersed with the fibrous tissue of the aneurysm Another proposed explanation is a window effect wherein unopposed normal repolarization of the posterior myocardial wall is displayed in leads over the aneurysm A degree of residual ST segment elevation after aneurysmectomy may be related to the surgical technique That is not all of the fibrous tissue is excised a perimeter of scar being retained in order to provide a firm suture line Probably the employment of additional diagnostic techniques such as postoperative ventriculography myocardial scanning or surface mapping may add further information on this phenomenon

There are few detailed reports of the effects of ventricular aneurysm surgery on the electrocardiogram and their conclusions are not in agreement Cokkinos and colleagues analyzed 26 cases and found a significant postoperative decline of the magnitude of ST elevation in the lead with the greatest elevation Prior to surgery there were four cases with no ST elevation and there were eleven cases with none a few days after surgery On the other hand Dolgin and associates found no significant difference in the sums of ST elevation 117.9 days (range 4 to 211 days) following surgery in 29 patients In 12 cases the ST elevation was worse and in 10 it was improved Richter and co workers describe the ECG changes after left ventricular aneurysmectomy in 20 patients including three with inferoposterior aneurysms. Of fourteen with functional and/or hemodynamic improvement eight had less ST elevation In the six unimproved patients postoperative ST elevation did not change significantly From these three studies involving 75 patients as well as from the present investigation it seems clear that a decline of ST segment elevation after aneurysm surgery is not a useful guide to clinical status—particularly when applied to individual patients

As expected clinical improvement followed resection of left ventricular aneurysm in most of the patients of this study although a parallel regression of the diagnostic ECG feature was not a consistent finding Though there was a statistically significant reduction of total ST elevations for the entire group postoperative ST decline occurred in only 16 (24.2 per cent) of clinically improved patients and in 17 (36 9 per cent) of those with improved x rays Moreover ST improvement was seen in three of the eight clinically unimproved patients In patients with ventricular aneurysm following myocardial infarction ST segment elevation persists affected little by surgical intervention Therefore analysis of ST segments in the standard chest leads following left ventricular aneurysm surgery in these patients did not provide reliable indicators of clinical or radiologic improvement

Summary

Post myocardial infarction aneurysms are often accompanied by persistent ST segment elevations To determine whether or not these ST segments regress following successful surgery for left ventricular aneurysms serial electrocardiograms were studied in 74 patients and compared to changes of heart size and NYHA Functional Class The mean postoperative follow up period was 18 2 months (range 3 to 52 months) The mean precordial ΣST elevation preoperatively

was 5 27 mm and 4 71 mm after surgery ($P < 0.025$) For the highest ST segment of an individual lead the mean values were 1 9 mm before surgery and 1.88 mm postoperatively ($P > 0.1$) Although clinical improvement occurred in 66 (89 2 per cent) by NYHA class and x ray evidence of improvement was seen in 46 (62 2 per cent) a degree of ST elevation remained in all cases and was less elevated in only 19 (25 7 per cent) After surgery for left ventricular aneurysm ST segments tend to remain elevated with little apparent relation to reduction of heart size or clinical improvement

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Evaluation of aortocoronary venous bypass grafting for prevention of cardiac arrhythmias

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In patients with coronary artery disease (CAD) ventricular arrhythmias may herald sudden death[1,2] Their severity and rate of occurrence being related to the extent of coronary obstruction and myocardial fibrosis and the degree of ischemia[3] it appears reasonable to assume that successful coronary revascularization should suppress these arrhythmias Indeed improvement of ventricular arrhythmias has been reported following resection of aneurysms particularly if combined with aortocoronary bypass (ACB)[8-11] However opinions on the effect of ACB alone are conflicting[1] Several authors described beneficial effect of surgery[12] while others reported no effect[2] or even a worsening of arrhythmias after ACB The incidence of sudden death in CAD has been reported to be lower in patients who were treated surgically[3] The purpose of the present prospective investigation was therefore to study the influence of ACB on cardiac arrhythmias using ambulatory Holter monitoring

Patients and methods

Patients We examined 27 patients (24 men and three women with a mean age of 53 8 years) who underwent ACB for refractory angina pectoris and/or significant left main coronary artery stenosis Pre and postoperative data on standard ECG hemodynamic and angiographic findings as well as perioperative complications are shown in Table I Coronary angiography revealed single-vessel disease in seven patients double vessel disease in 14 triple vessel disease in five patients, and left main stenosis in one patient Ventriculography disclosed dyskinetic areas in seven patients Patients with ventricular aneurysm evidenced by systolic and diastolic bulging were not included in the study ACB was routinely carried out using saphenous vein transplants 91 4 per cent of the diseased vessels were grafted As part of another investigation 20 out of these 27 consecutive patients bearing 39 grafts were restudied 2 weeks postoperatively At this point three grafts (7 7 per cent) were occluded and one graft could not be visualized at angiography

Holter monitoring Eight hour Holter monitoring and analysis were carried out as previously described between 8 A M and 4 P M using non-computerized Holter Avionics equipment A monitoring period of 8 hours was deemed to be sufficient for detecting a majority of the arrhythmias, since it was shown previously that approximately 81 per cent of cardiac arrhythmias can be recorded during this time Daytime recording was chosen in the light of earlier reports demonstrating a predominance of ventricular arrhythmias during the day The first ECG was recorded 8 days preoperatively and the second 100

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was 5 27 mm and 4 71 mm after surgery ($P < 0.025$) For the highest ST segment of an individual lead the mean values were 1 9 mm before surgery and 1 88 mm postoperatively ($P > 0.1$) Although clinical improvement occurred in 66 (89 2 per cent) by NYHA class and x ray evidence of improvement was seen in 46 (62 2 per cent), a degree of ST elevation remained in all cases and was less elevated in only 19 (25 7 per cent) After surgery for left ventricular aneurysm ST segments tend to remain elevated with little apparent relation to reduction of heart size or clinical improvement

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Class II and eight patients (29 6 per cent) in Class III At the time of the postoperative recording 10 patients (37 0 per cent) belonged to Class I 13 patients (48 1 per cent) to Class II and four patients (14 8 per cent) to Class III (Fig 1) Analysis with the chi square test disclosed that over all classification of arrhythmias has not changed significantly following ACB Moreover even when patients with significant ventricular arrhythmias (Class III) are considered apart we found no statistical evidence suggesting qualitative improvement by the operation (sign test $p > 0.1$) Evaluation by the chi square test showed that age preoperative infarction pre and postoperative hemodynamic data and wall movement number of vessels involved completeness of revascularization perioperative complications and graft patency had no significant influence on cardiac rhythm

Discussion

In earlier investigations it has been shown that prevalence and severity of ventricular arrhythmias are correlated with the degree of vascular involvement and ischemia in patients with coronary artery disease Thus it seems logical to assume that correction of myocardial ischemia by ACB should also tend to abolish ventricular dysrhythmias In agreement with other studies the present investigation does however not provide statistically valid evidence of such a beneficial effect by coronary revascularization Although arrhythmias show large spontaneous variations in individuals they probably cancel out in groups of patients

In our subjects age preoperative myocardial infarction and its localization preoperative and postoperative hemodynamic data and wall movement number of vessels involved completeness of revascularization perioperative complications and graft patency did not identify patients in whom cardiac arrhythmias were favourably influenced by the operation This is in agreement with Tilkian and colleagues and De Soyza and associates [1] who found no influence of graft patency on the prevalence of ventricular arrhythmias However the small size of our group does certainly not permit us to draw definite conclusions When attention is focused on the eight patients with clinically more relevant arrhythmias before surgery (Class III) it is noteworthy that five of them moved into Class I or II as a

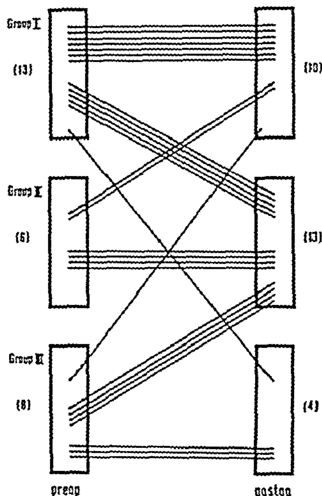


Fig 1 Pre- and postoperative classification of cardiac dysrhythmias in 27 patients who underwent aortocoronary bypass operation reveals no significant influence of surgery on arrhythmias. Class I NRS ± occ APBs Class II less than five unifocal VPBs per minute Class III more than five VPBs per minute multifocal VPBs, VPBs in a row or VT NSR = normal sinus rhythm APBs = atrial premature beats VPBs = ventricular premature beats VT = ventricular tachycardia ACB = aortocoronary bypass surgery

result of the operation Conversely only one patient moved into Class III after ACB This slight improvement though is not statistically significant (sign test $p > 0.1$) Assuming identical distribution one would have to examine 45 patients with arrhythmias of Class III before the observed tendency would become significant at the 5 per cent level. We believe that further investigation is needed before conclusions on the influence of ACB on major ventricular arrhythmias can be drawn

We feel that at the present time ventricular arrhythmias alone constitute no indication for aortocoronary bypass surgery

Summary

The influence of ACB on cardiac arrhythmias was examined in 27 patients Eight hour Holter monitoring was performed 8 days preoperatively and 100 days postoperatively Arrhythmias were divided into 3 groups (Class I NSR ± occasional APBs Class II less than five unifocal VPBs per minute, Class III more than five VPBs per minute multifocal VPBs VPBs in a row or VT) Preoperative classification disclosed that 13 patients (48 1 per cent) were in Class I six patients (22 2 per cent) were in Class II and eight patients (29 6 per cent) were in Class III The corresponding values after surgery were 10 patients (37 0 per cent) 13 patients (48 1 per cent) and four patients (14 8 per cent) These differences were not statistically significant ($p > 0.1$) In view of the tendency of arrhythmias of Class III to improve after ACB we feel that further investigations in this area are needed At the present time ventricular arrhythmias alone constitute no indication for bypass surgery

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Sudden coronary death A postmortem study in 208 selected cases compared to 97 "control" subjects

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The different patterns of death had been already categorized in 1707 by Lancisi when he reported an epidemic of sudden death in Rome Indeed this absolutely complete cessation of animal movements and thus departure of the soul from the body even though it happens at all times more swiftly than itself is nevertheless divided for the sake of common parlance and for greater clarity of teaching into natural untimely and violent death and these again into slow and sudden deaths into those are foreseen and forefelt and finally into such as are unforeseen unperceptible and unexpected Lancisi s distinction is still up to-date when we try to profile the natural history of so called coronary heart disease (CHD) in general and sudden coronary death (SD) in particular At least part of the divergencies among the numerous reports on this modern epidemic may likely be due to the lack of differentiation between foreseen and forefelt and unforeseen and unexpected cases

The present uncertainties on the significance of postmortem findings require us (1) to categorize the patho morphology pertinent to the natural history of the various patterns of CHD (angina myocardial infarction and sudden death) (2) exclude any possible overimposed effects secondary to iatrogenic factors and (3) to control the general incidence of the morphologic changes

The present study is an attempt to investigate and to discuss the significance of the pathologic findings observed in untreated cases of sudden coronary death not previously recognized as CHD patients and to compare them with a control population

Method

According to the Italian law a postmortem examination has to be performed on all subjects not under medical care who die suddenly as well as on those who die by accident From 1967 208 witnessed cases of coronary sudden death and 97 witnessed cases of accidental death fulfilling the following criteria were selected in the Forensic Institute University of Milan Italy

1 A reliable family and personal history was obtained by a careful interview of the witnesses and the members of the family according to a specific protocol

2 Death occurred before any medical assistance therapy or resuscitation maneuvers could be given

3 Physical and working activity at the time of death had been usual and normal

4 A disease which could be related to the death including a manifest pattern of CHD was absent from the history

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Table I Histologic pattern in different types of myocardial necrosis in CHD

Myocardium	*Coagulation necrosis*	*Coagulative myocytolysis*	*Colliquative myocytolysis*
Functional status	*Irreversible relaxation (atonic death) + stretching by intraventricular pressure*	*Irreversible contraction (tetanic death)*	*Progressive loss of function (failing death)*
Muscle fiber	Early thinning	Normal or swollen	Increasing edema—vacuolization
Nucleus	Elongation pyknosis progressive fading	Normal	Normal
Myofibrils	Elongated sarcomeres in normal registered order even in late stage	Rhexis—Anomalous irregular cross band formations (coagulation of hypercontracted sarcomeres)	Progressive disappearance "empty cell" (colliquation)
Vessels	Secondary wall degeneration and thrombosis	Normal	Normal
Infiltration	Massive polymorphonuclear exudation	No early infiltrates Possible late lymphocytes	No infiltrates
Extension—Location	In general unique massive focus of different size internal to transmural	Multiple (mono- or pluricellular) disseminated or confluent foci of different size in any muscular layer	Focal subendocardial and perivascular progressively spreading
Irreversible within	At least [illegible]0-60 min	Few minutes	?
Healing	In all the three different types	Remotion by macrophages. Collagenization of empty sarcolemmal tubes.	
Frequency in CHD			
Acute infarct	100%	100% external layer of early infarct [illegible]% in normal myocardium	43%
Sudden death	[illegible]% histologically demonstrated	[illegible] unique demonstrable lesion 86% including cases with coagulation necrosis	8%

5 Subjects not under medical care and not taking drugs of any type who die without having consulted a doctor at least one week before death

6 Absence of significant pathologic findings both acute and chronic, in all the organs other than the heart

7 Absence of cardiac pathologic findings other than coronary atherosclerosis myocardial necrosis or fibrosis associated or not with cardiac hypertrophy

8 Negative tests for poisoning or intoxication provided for the accidental death cases due to suicide

All the cases were selected at random independently of the degree of coronary atherosclerotic damage The obvious result of this type of selection will be limited and questionable clinical information for the following reasons first the subjects died outside a hospital and without any control by medical personnel second their clinical history was obtained from persons (witnesses and members of the family) not qualified in a medical sense third the frequent habit of people to minimize their symptomatology Nevertheless we have distinguished cases with an apparently negative clinical history (106 subjects) from those in whom prodromata—episodes of chest and/or arm pain dyspnea arm paresthesia vertigo—suggestive of latent CHD were present (102 subjects) These two groups were arbitrarily defined as sudden unexpected death (SUD) and sudden expected death (SED) In the accidental death cases (AD) the death was due to trauma or CO intoxication

The autopsy was performed between 14 to 74 hours after death the body being kept in a refrigerator at 4° C The removed heart was carefully washed and weighed and then opened according to the classical method of Prausnitz

Coronary arteries The diameter of the coronary ostia were measured by a calibrated conus The main coronary arteries and their subepicardial branches to a diameter of 1 mm were cross sectioned at 3 mm intervals along their whole course Samples for histologic examination were systematically taken at the origin of the left main coronary artery (LMA) left anterior descending branch (LADB) left circumflex branch (LCXB) right coronary artery (RCA) posterior descend

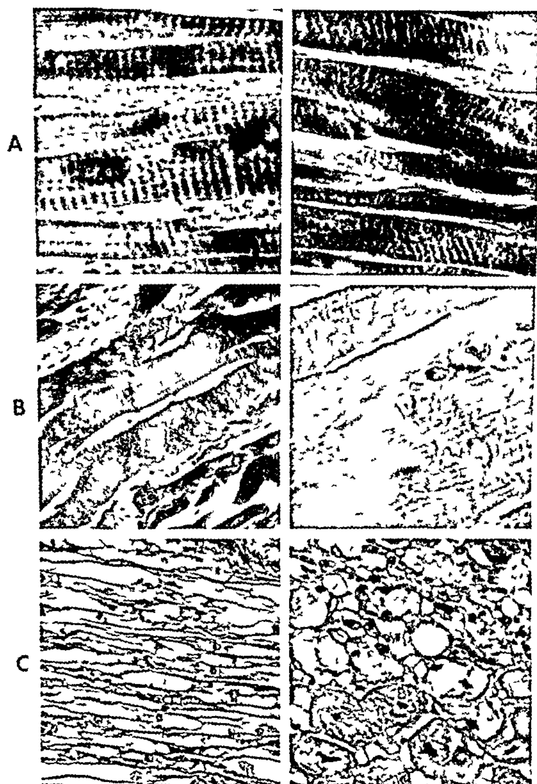


Fig 1 A through C *Different types of myocardial cell damage* A Coagulation necrosis with apparently undamaged myofibrillar apparatus The *sarcomeres are in register* *Left* 14 days infarction *right* 25 days infarction (Hematoxylin and eosin stain original magnification ×550) *B* Coagulative myocytolysis Primary myofibrillar damage with rhexis and anomalous band formation (*Left* PTAH stain original magnification ×220 *right* Hematoxylin and eosin stain original magnification ×6?0) *C* Colliquative myocytolysis Colliquative disappearance of the myofibrils *Left* "empty" myocells in longitudinal section (PAS stain original magnification ×160) *Right* transverse section—different stages of vacuolization (Hematoxylin and eosin stain original magnification × 1?0)

ing branch (PDB) second distal LADB and at the origin and at the middle portion of the posterior segment of the RCA Furthermore the length of any stenosis was measured and all the sections involved by a stenosis were histologically examined Intimal thickening was calculated in microns by a micrometer as was the average diameter at the site of maximal lumen reduction The degree of an old stenosis was referred to as a percentage of the average diameter of the normal vessel[2] The pattern of stenosis at the site of maximal lumen reduction was defined as con centric when the residual lumen was centrally located or when in the lateral position but still encircled by pathologic fibrous–atheromatous tissue and 'semilunar if part of the vessel wall was normal Finally atheromatous and fi brous types of stenosis were distinguished according to their prevalent composition A thrombus was defined as 'early when no reac tion was found recent when early sprouting of endothelial cell and capillary growth to different stages of more advanced organization were seen and old when organized A thrombus was judged as occlusive or mural when filling more or less than 50 per cent of the lumen respectively In general mural thrombi were a thin lamina of fibrin platelet material overlaying the internal surface of a plaque

Myocardium In each heart samples of the entire wall at the basal median and apical levels of the anterior lateral and posterior walls of both left and right ventricles (including the papillary muscles) of the interventricular septum of the left and right atria and of the conduction system (Sinus node A V node bundle of His and the origin of its branches) were systematically exam ined Furthermore any damaged area seen by the naked eye was also examined

Acute irreversible myocardial damage was distinguished as coagulation necrosis coagulative myocytolysis and colliquative myocytolysis[3] The main morphologic changes of these three types of necrosis are summarized in Table I (Fig 1) Coagulation necrosis–the pathogno monic lesion of an infarct–and myocardial fibro sis were defined as minimal when only a few microscopic foci were histologically detected moderate when the lesion involved less than half of the cardiac wall in one or two areas and extensive when the damage was more diffuse Coagulation necrosis was estimated 6 to 12 hours old when thinning of the myocardial cells and elongation of the nuclei were associated with early polymorphonuclear cell infiltration the subsequent stages being evaluated according to the classic criteria Fibrosis was considered old when formed by a dense hypocellular–vascular scar tissue and recent when still showing a large number of fibroblasts and vessels in absence of residual necrotic myocardium Myocytolysis both coagulative and colliquative was regarded as minimal when few foci (less than five) were observed only in one location moderate when few foci were observed in less than three different areas and extensive when the lesion was more widespread Coagulative myocytolysis was de fined early' when myofibrillar rhexis and anom alous cross bands in hypercontracted myocells were seen alveolar when the allo sarcoplasmic material was removed leaving empty sarcolem mal tubes with macrophages and scarring when the previous stages were associated with collagenization Samples of all main organs were also taken for histological examination

All the data were reported on original cards and processed by an IBM 370/168 computer and the statistical evaluation was carried out by both parametric and non parametric tests

In the present report we will limit our presen tation and discussion to the incidence and the relationship between (1) chronic and acute morphologic obstructive changes of the subepi cardial coronary arteries and their main branches (2) non inflammatory irreversible dam age of the myocardium and (3) survival time activity symptoms and heart weight

Results

Age and sex (Table II) Out of 208 SD cases 182 were males and 26 were females (M/F = 7) In the AD subjects 88 were males and nine were females (M/F = 9 7) The SD showed the highest incidence in the sixth and seventh decades for males and in eighth decade for females Because the population of females was so small data were considered without regard to sex difference

Old coronary stenosis (Table II) A severe lumen reduction ($\geq$ 70 per cent) due to athero sclerotic changes of at least one of the main subepicardial arterial vessels was present in 38 AD subjects (39 1 per cent) and in 157 SD subjects (75 4 per cent) being multiple in 12 and in 104 subjects respectively In 28 SD cases (13 4

Table II Age and sex in relation to coronary damage

Age	Sex		% maximal lumen reduction						Severe stenosis (≥ 70%) in			
	M	F	< 50	50-69	70-79	80-89	≥ 90	Total	1	2	≥ 3 vessels	Total
S D												
< 20	4	2	6	–	–	–	–	6	–	–	–	–
20-29	6	1	3	–	–	2	2	7	–	4	–	4
30-39	20	2	5	4	1	7	5	22	7	2	4	13
40-49	31	2	4	3	2	9	15	33	6	7	13	26
50-59	63	5	4	8	10	19	27	68	19	22	15	56
60-69	41	4	4	5	8	11	17	45	12	16	8	36
> 70	17	10	2	3	8	5	9	27	9	9	4	22
Total	182	26	28	23	29	53	75	208	53	60	44	157
A D												
< 20	–	–	–	–	–	–	–	–	–	–	–	–
20-29	–	1	1	–	–	–	–	1	–	–	–	–
30-39	9	–	4	4	1	–	–	9	–	1	–	1
40-49	11	2	8	2	2	1	–	13	3	–	–	3
50-59	27	1	11	7	5	4	1	28	7	2	1	10
60-69	20	3	2	9	5	4	3	23	8	3	1	12
> 70	21	2	2	9	6	4	2	23	8	3	1	12
Total	88	9	28	31	19	13	6	97	26	9	3	38

Table III Distribution of different degree of stenosis in main coronary arteries

Stenosis %	LMA	LADB	LADB1	LADB2	LCXB	RCA	RCA I	RCA II 1	RCA II 2	PDB
208 SD Cases										
< 50	83	24	48	35	44	27	49	48	31	11
50-69	40	51	65	52	37	36	51	38	27	13
70-79	7	36	30	28	27	27	22	15	14	9
80-89	3	43	25	28	29	43	28	17	15	2
≥ 90	1	39	20	24	27	40	18	9	14	1
Total	134	193	178	167	164	172	167	127	101	36
97 AD Cases										
< 50	32	31	41	17	28	24	34	22	13	4
50-69	7	25	22	18	16	30	26	12	13	2
70-79	–	16	12	11	4	11	7	2	3	–
80-89	–	11	3	9	1	4	2	3	1	–
≥ 90	–	1	1	–	3	2	1	1	–	–
Total	39	84	79	55	52	71	70	40	30	6

LMA = left main artery LADB = left anterior descending branch 1 superior 2 middle tract LCXB = left circumflex branch RCA = right coronary artery I anterior II posterior 1 and tract PDB = posterior descending branch.
In any vessel or segment only one stenosis with maximum lumen reduction is considered.

per cent) the lumen reduction was less than 50 per cent while it was between 50 and 69 per cent in 23 (11 per cent) In AD and SD groups the distribution of chronic coronary damage was homogeneous in different decades

The right coronary artery (RCA) and the left anterior descending branch (LADB) were the more compromised vessels in the two groups (Table III) being more frequently damaged in AD subjects ($\chi^2 = 7.05$ $P < 0.05$) A similar incidence of severe stenosis (≥ 70%) was found in the superior and middle portion of LADB The left circumflex branch was the third most compromised vessel while the left main trunk (11 SD cases) and the posterior descending branch (12 SD cases) showed a severe stenosis only in about 5

Table IV Thrombosis grade length and type of stenosis

Atherosclerotic plaque	*Thrombosis* — *Acute* — *Occlusive*	*Acute* — *Mural*	*Old* — *Occlusive*	*Old* — *Mural*	*Total stenosis* — *SD* 208	*Total stenosis* — *AD* 97
Stenosis %						
< 50	–	–	–	–	337	191
50-69	–	2	–	–	310	116
70-79	5	3	–	–	143	39
80-89	15	10	5	3	145	19
≥ 90	12	[illegible]	7	–	113	6
Total	32	22	12	3	1048	371
Severe stenosis (≥ 70%)					Total Severe stenosis	
Length (mm)						
≤ 5	2	2	2	–	48	2
6-20	6	6	3	1	139	24
> 20	24	14	[illegible]	2	214	38
Total	32	22	12	3	401	64
Type (≥ 70% stenosis)						
concentric	30	20	12	3	345	43
Semilunar	2	2	–	–	56	21
Total	32	22	12	3	401	64
Fibrous	8	4	5	1	216	38
Atheroma	24	18	[illegible]	2	185	26
Total	32	22	12	3	401	64

per cent The total number of all stenoses was 371 in AD and 1048 in SD The total number of *severe stenoses (≥ 70 per cent) was 64 401 respec*tively The length of the severe stenosis and its type did not show any significant divergence in the two groups except for a higher frequency of the semilunar type of stenosis in AD subjects (χ^2 = 16 27 P < 0 001) (Table IV)

An *acute occlusive thrombus* (Table IV) was detected in 32 of 208 SD cases (15 3 per cent) It was early in 16 subjects and recent in the other 16 The distribution of acute occlusive thrombi was homogeneous with respect to the *degree of stenosis* the number of involved vessels and the decades However the frequency of the thrombus was significantly higher with the increasing survival time (χ^2 = 5 25 P < 0 025 for the trend) Out of these 32 cases in 21 an infarct was not demonstrable In eight of the latter the thrombus was recent antedating by days the sudden death An acute mural thrombus was demonstrated in 22 cases an old occlusive thrombus in 12 while an old mural thrombus was seen in three SD cases All thrombi except two mural thrombi were located in an area of severe stenosis (≥ 70 per cent) Furthermore the frequency of thrombus tended to correlate with an increasing length a concentric pattern and an atheroma*tous type of stenosis A second thrombus* was observed in 16 SD cases (three acute occlusive five acute mural four old occlusive and four old mural) All of the second thrombi but one were located in a severe and long stenosis Among the AD subjects in only one instance was there an acute mural thrombus located in an 80 per cent stenosis

Irreversible myocardial damage (Table V) The pathognomonic finding of irreversible damage of an infarct namely a coagulation necrosis was documented histologically in 35 SD cases (16 8 per cent) This lesion was extensive in eight moderate in 16 and minimal in 11 Its presence and extension did not correlate with the degree and number of severe stenoses An acute occlusive thrombus was observed in 11 of these 35 cases (31 4 per cent) The coagulation necrosis was judged to be in the early stage (6 to 12 hours) in 14 while in the remaining subjects it was considered older than 2 days In six instances this necrosis showed different stages in two different areas In 32 cases the coagulation necrosis was associated with old myocardial fibrosis

Table V Myocardial damage stenosis and acute occlusive thrombosis

	Stenosis %				*≥ 70 % in*								
	< 50		*50 69*		*1*		*2*		*≥ 3 Vessels*		*Total*		*SD Thrombus*
Myocardial damage	*SD*	*AD*	*SD*	*AD*	*SD*	*AD*	*SD*	*AD*	*SD*	*AD*	*SD*	*AD*	
Coag necrosis													
Minimal	–	–	–	–	3	–	4	–	4	–	11	–	1
Moderate	–	–	–	–	4	–	8	–	4	–	16	–	6
Extensive	1	–	1	–	5	–	1	–	–	–	8	–	4
Total	1	–	1	–	12	–	13	–	8	–	35	–	11
Coag myocyt													
Minimal	15	8	8	3	16	2	25	3	24	–	88	16	7
Moderate	3	–	3	1	8	–	14	–	10	–	38	1	9
Extensive	4	–	1	1	8	1	9	–	1	–	23	2	9
Total	22	8	12	5	32	3	48	3	35	–	149	19	25
Early	18	7	9	2	21	3	25	2	22	–	95	14	9
Alveolar	–	1	1	3	7	–	9	–	11	–	28	4	9
Scarring	4	–	2	–	4	–	14	1	2	–	26	1	7
Total	22	8	12	5	32	3	48	3	35	–	149	19	25
Coll myocyt													
Minimal	–	–	–	–	1	–	5	–	10	–	16	–	1
Fibrosis													
Minimal	16	11	15	18	32	11	24	4	8	2	95	46	15
Moderate	–	1	4	1	11	1	15	2	16	–	46	5	4
Extensive	–	–	1	–	1	–	12	–	15	–	29	–	5
Total	16	12	20	19	44	12	51	6	39	2	170	51	24

Coagulative myocytolysis was the most frequent acute lesion found It was observed as a unique acute lesion in 149 (71 6 per cent) cases of SD and in 19 AD cases (19 6 per cent) In all but three of the latter cases the lesion was minimal, while in SD subjects it was moderate to extensive in 29 3 per cent (Fig 2) In most of the AD subjects and in about two thirds of the sudden death cases this type of necrosis was early in 13 4 per cent of SD cases and in 4 2 per cent of AD cases it was alveolar while it was scarring in 12 5 and one per cent respectively Among the 28 SD cases with normal coronary arteries or a lumen reduction less than 50 per cent coagulative myocytolysis was observed in 22 cases (78 5 per cent) In all the 35 SD cases with coagulation necrosis coagulative myocytolysis was seen at the perimeter of the infarct and in 29 subjects *(82 8 per cent) in the normal myocardium If the* latter cases are included the total frequency of coagulative myocytolysis in all 208 SD subjects was 85 5 per cent No relationship was found between the presence and extension of coagulative myocytolysis and the degree of coronary *damage as well as the presence or absence of a* thrombus

In only 16 (7 6 per cent) of the 208 SD cases minimal foci of subendocardial colliquative myocytolysis were observed All but two cases *belonged to subjects with pathological heart* weight (≥ 500 gm) and extensive old fibrosis

Old myocardial fibrosis was found in 170 SD (81 7 per cent) and in 51 AD cases (52 6 per cent) In general the AD subjects showed minimal fibrosis in only five (5 2 per cent) cases was there a single median focus of fibrosis In contrast in the SD group the fibrosis was moderate in 22 1 per cent and extensive in 13 9 per cent Minimal fibrosis was not related to an increasing degree of coronary lesions in any group Conversely moderate and extensive fibrosis tended to increase with *an increasing number of vessels with severe steno*sis in SD No relationship was found between the extension of coagulation necrosis as well as the frequency of acute occlusive thrombus and the extension of old myocardial fibrosis

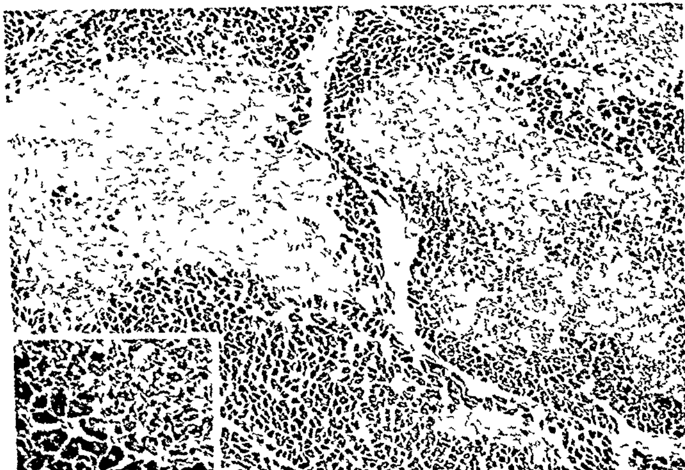


Fig 2 Extensive coagulative myocytolysis in a 54 year-old man who died suddenly (PTAH stain original magnification ×70 inset original magnification ×300)

Recent myocardial fibrosis was seen in 31 SD cases (isolated in five associated with old fibrosis in 16 and old fibrosis + coagulation necrosis in 10 the lesion being located in different areas) Most of these foci were minimal only two being extensive and two median

The different patterns of irreversible acute and old myocardial damage were seen more frequently in the left ventricle followed by the interventricular septum and the right ventricle Acute irreversible damage was not seen in the conduction system and only in 18 SD cases were micro foci of old myocardial fibrosis observed in the latter

Heart weight (Table VI) In 87 cases (41 8 per cent) of SD and in 10 (10 3 per cent) AD cases the weight of the heart was pathological (≥ 500 gm) No correlation was found between maximum lumen reduction number of severely stenosed vessels frequency of thrombus incidence/extension of coagulation necrosis coagulative myocytolysis myocardial fibrosis and increasing heart weight

The survival time (Table VII) was less than 10 minutes in 151 SD cases within one hour in 47 and within 3 hours in 10 cases In the AD group the death occurred within 10 minutes in all people dying from trauma and less than 6 hours in those dying from CO intoxication About half of the SD subjects were active (52 working 44 walking 13 driving) at the time of death while the other half were sleeping[7] or resting [77] One hundred three SD subjects were found unconscious or at least unable to express their symptoms In the remaining cases chest pain was reported in 48 dyspnea in 29 while arm paresthesia or vertigo were present in a few instances No relationship was found between survival time activity and symptoms before death as well as between these parameters and the degree of coronary and myocardial damage and heart weight

Prodromata A comparison between 102 sub

Table VI Heart weight stenosis and myocardial damage

Heart uıght (gm)	Total cases	Stenosıs %		≥ 70% ın			Coag necrosıs	Coag myocyt	Fibrosıs
		< 50	50 69	1	2	≥ 3 Vessels			
SD									
< 400	51	13	3	16	14	5	9	36	37
400 499	70	4	3	19	22	22	14	48	50
500 599	43	4	7	7	14	11	5	34	41
600 699	25	3	4	8	5	5	3	18	24
700 799	12	4	2	1	4	1	4	8	11
≥ 800	7	–	4	2	1	–	–	5	7
Total	208	28	23	53	60	44	35	149	1 0
AD									
< 400	54	18	14	15	5	2	–	8	28
400-499	33	6	14	9	3	1	–	9	16
500-599	9	3	3	2	1	–	–	2	7
600 699	1	1	–	–	–	–	–	–	–
Total	97	28	31	26	9	3	–	19	51

jects with (SED) and 106 without (SUD) prodromata showed a statistically significant higher frequency of (1) acute occlusive thrombus ($\chi^2 = 4\ 78$ $P < 0\ 05$) in the SUD group (2) stenosis greater than 90 per cent ($\chi_2 = 6\ 34$ $P < 0\ 05$), (3) triple or more severe (≥ 70 per cent) stenosis ($\chi = 5\ 67$ $P < 0\ 025$) (4) moderate/extensive myocardial fibrosis ($\chi = 10\ 24$ $P < 0\ 01$) and (5) pathological heart weight ($\chi = 10\ 16$ $P < 0\ 005$) in the SED group (Table VIII)

Discussion

Coronary heart disease is generally interpreted as due to absolute or relative critical reduction of the nutrient blood flow to the myocardium This interpretation implies that (1) ischemia should be proportional to the degree and number of the coronary stenoses and (2) the coronary tree is an end arterial system without an effective collateral compensation when acute events occur This is a concept apparently supported by the experimental acute coronary occlusion which results in sudden death or in infarct if the animal survives Accordingly sudden death and infarct are considered as synonymous the lack of demonstrable coagulation necrosis in the former being due to the rapidity of death The present data however question this classic pathogenic view and its postulates

Distribution and significance of old stenosis The first point to be stressed is that sudden death may happen in the absence of or with minor lumen reduction One may argue if the 28 cases (13 4 per cent) in which no acute or old ischemic morphologic factors were seen can be defined as coronary' and then be included in this study We believe that this is correct since they showed an identical distribution of acute myocardial damage and pathologic heart weight as the other cases The second point is that there is no critical grade of obstruction responsible for the sudden death In other words one may die suddenly as the first episode of CHD independently of the degree of severe stenosis (70 to more than 90 per cent) and the number of the involved vessels The third point is that the coronary lesions are signs of an old process which was silent for months or years before sudden death in people living a normal life style Finally the findings in the normal AD subjects show that a severe stenosis even multiple in nature can be ineffective in producing sudden death

All the previous facts point out the absence of a linear cause-effect relationship between stenosis and sudden death In addition they suggest the functional adequacy of the highly enlarged collaterals seen postmortem in these conditions[4] At present there is no proof that the onset of CHD is due to an acute failure of these collaterals

Distribution and significance of an acute occlusion In the majority of SD subjects we were unable to demonstrate any morphologic occlusive cause In only 32 cases (15 3 per cent) was an acute occlusive thrombus found This low figure is in agreement with previous reports[6, 7] Furthermore the thrombus was always located at the

Table VII Survival, activity, and symptoms before sudden death in relation to coronary and myocardial damage and heart weight

	Total cases	Stenosis				Ac. occl. thrombus	Coagulation necrosis	Coag. myocyt.	Fibrosis	Heart weight ≥ 500 gm
		≤ 69%	≥ 70% in							
			1	2	≥ 3 vessel					
Survival										
< 10 min	151	41	39	41	30	18	25	110	123	68
10-60 min	47	9	11	17	10	11	8	33	37	18
> 60 min	10	1	3	2	4	3	2	6	10	1
Total	208	51	53	60	44	32	35	149	170	87
Activity										
Working	52	10	22	11	9	5	6	37	40	22
Walking	44	7	11	13	13	5		37	40	17
Driving	13	–	1	9	3	1	2	9	14	5
Sleeping	22	9	5	5	3	4	5	13	20	9
Resting	72	23	12	21	16	17	14	51	54	33
Unknown	5	2	2	1	–	–	1	2	2	1
Total	208	51	53	60	44	32	35	149	170	87
Symptoms										
Angina	48	4	20	12	12	11	9	32	35	16
Dyspnea	29	12	6	8	3	3	6	24	25	14
Paresthesia	3	–	1	2	–	2	1	3	3	–
Vertigo	4	–	1	3	–	–	1	4	4	2
Unknown	124	35	25	35	29	16	18	86	103	55
Total	208	51	53	60	44	32	35	149	170	87

level of severe stenosis, a finding identical to that seen in acute infarcts.[13] Because of the preexistence of functioning collaterals in the presence of an old severe stenosis, the thrombus may be ineffective in reducing the blood flow. This assumption is substantiated by the SD cases with a "recent" thrombus without infarct. In fact an organizing thrombus antedates the sudden death for such a length of time that if the thrombus is the cause, an infarct should be documented. Spasm of a coronary artery or other mechanisms may increase the peripheral resistance distal to the stenosis. In turn, a further blood stagnation with secondary thrombus formation within the residual lumen may be expected—a hypothesis supported by the frequent occlusion of a surgically bypassed stenosis, the vein graft being the equivalent of native collaterals at very high pressure.

Distribution and significance of the myocardial damage. In most SD cases an acute lesion different from that pathognomonic of an infarct was found. This type of necrosis—similar if not identical to Zenker necrosis of skeletal muscle and variously named (myocytolysis, sarcolysis, myofibrillar degeneration, miliary infarct, coagulative myocytolysis)—corresponds to primary myofibrillar damage in myocardial cells dying in irreversible hypercontraction. It can be seen in a variety of both human and experimental conditions and constitutes the characteristic damage induced by catecholamines or found in pheochromocytoma. Due to the type of selection, the possibility that in our material this finding may have an iatrogenic nature (catecholamine infusion, cardiac massage, electrical defibrillation

Table VIII Significant differences between cases with (SED) and without (SUD) prodromata

	≥ 90% Stenosis	≥ 3 vessels ≥ 70 stenosis	Heart weight ≥ 500 gm	Fibrosis		Thrombus Ac. Occl.
				Mod.	Ext.	
SUD (106)	34	16	33	13	11	22
SED (102)	41	28	54	33	18	10
Total (208)	75	44	87	46	29	32

etc) can be excluded On the other hand it has been observed with the same frequency in the external layer of an infarct (coagulation necrosis) and in the surrounding normal myocardium[3] Since this lesion develops very quickly and is already visible within five minutes after experimental coronary occlusion[9] the following two possibilities may be considered in sudden death This necrosis may be the first sign of (1) non detectable infarct, or (2) a primary sympathetic disorder linked with ventricular fibrillation and not necessarily associated with an infarct The cases with advanced stages (alveolar and/or scarring) of this necrosis not associated with an infarct as well as the cases resuscitated by defibrillation without subsequent evidence of an infarct[21] seem to confirm that sudden death is not always synonymous with the latter Furthermore because of its very high frequency coagulative myocytolysis may also be responsible for myocardial fibrosis particularly when microfocal or confluent

In few SD cases only minimal occasional foci of colliquative myocytolysis were seen The practical absence of this lesion—characteristic of the cardiomyopathies with failure of the cardiac pump[19]—is an agreement with the normal activity of the examined subjects and emphasizes that failure of the pump does not seem to have a significant pathogenic role when sudden death is the first fatal event of CHD

Comparison between unexpected and expected SD cases Most of the parameters considered showed a similar behavior in the two groups However the SED subjects showed a significant divergence particularly in respect of (1) a higher incidence of myocardial fibrosis (2) a greater frequency of pathologic heart weight and (3) a higher frequency of maximum degree of stenosis ($\geq$ 90 per cent) and triple vessel involvement—a behavior similar to that seen in subjects with an old infarct[5] These findings associated with the presence of symptoms in their history may indicate that SED subjects are more chronic subjects in whom both myocardial fibrosis and the pathological heart weight may be the result of a chronic sympathetic noxa Hypertrophy of the heart plus the typical lesion can be reproduced experimentally by catecholamines[12 21] The highest value of lumen reduction and triple vessel involvement in SED subjects as well as in chronic CHD patients may be due to secondary progressive mural thrombotic deposition in a stenosis already bypassed by collaterals[3] Finally, the finding of coagulative myocytolysis and myocardial fibrosis in some 'controls' may indicate a 'sympathetic' risk factor in these subjects

Summary

Two hundred eight witnessed subjects dying suddenly (SD) (151 in 10 minutes 47 in one hour and 10 in three hours) and 97 dying by accident (AD) were studied All these subjects had no clinical history of CHD They were at the time of death in their normal usual activity, and not under medical care No therapy before and resuscitation attempts after death were done The unique postmortem findings were coronary atherosclerosis and/or myocardial necrosis or fibrosis Coronary stenosis was absent or insignificant (< 50 per cent) in 28 median in 23 and severe ($\geq$ 70 per cent) in 157 (53 monovessel 60 double vessel 44 triple vessel or more) SD cases In AD the figures were 28 31 38 (26 nine and three) respectively Thirty two (15 3 per cent) SD subjects showed an acute occlusive thrombus located in a severe long concentric stenosis An infarct was demonstrable in 35 SD cases (11 plus occlusive thrombus) A necrosis resembling that induced by catecholamines was the unique acute myocardial lesion found in 149 SD subjects (72 per cent) This lesion was also present in 29 out of 35 subjects with an infarct (total 178 = 85 5 per cent) in 22 out of 28 SD cases with insignificant coronary damage and in 19 AD cases One hundred two SD cases with prodroma had a significant lower frequency of thrombi and a higher frequency of stenosis $\geq$ 90 per cent triple vessel involvement myocardial fibrosis and pathologic heart weight ($\geq$ 500 gm) These data suggest that (1) there is no proof that SD is due to a morphologic occlusive cause the thrombus being likely to be an ineffective event secondary to regional increased peripheral resistance in the presence of functioning collaterals, (2) there is no linear cause-effect relation between the degree of coronary damage and SD (3) a primitive sympathetic disorder may be responsible for ventricular fibrillation myocardial necrosis/fibrosis and cardiac hypertrophy—SD being not necessarily synonymous with infarct

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The prognostic value of the P wave morphology in the discharge ECG in a 5-year follow-up study after myocardial infarction

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The left ventricular post myocardial infarction performance is generally accepted as the main determinant of subsequent patient survival [1] The factors often used to describe the hemodynamic status after infarction have been based on the clinical examinations and/or chest x rays [2 5] The P terminal force (PTF) i e, the size of the negative portion of the P wave in chest lead V_1 was first studied in patients with chronic mitral valve disease and also in this laboratory in atrial septal defect[12] as well as in acute mitral regurgitation due to papillary muscle dysfunction in acute myocardial infarction [13] Recently PTF has been shown to be closely related to left ventricular dysfunction during the acute phase of myocardial infarction [1 15] There is one study in the literature regarding the relationship of PTF with the chronic survival after infarction

Other electrocardiographic (ECG) variables describing the atrial activity have also been used in studies on the survival after infarction [7 1] However the atrial electrocardiogram described by the PTF the frontal axis of the terminal P wave (PTFA) the P wave duration and atrial fibrillation have not been previously analyzed with regard to survival after infarction The present study investigates the relationship of these ECG variables to the survival during a 5-year follow up

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Study population and methods

The study population is from the Helsinki Coronary Register It comprises all cases of acute ischemic heart disease (AIHD) acute myocardial infarctions (AMI) and sudden coronary deaths (SCD) within its area The diagnostic category of each case is decided on the basis of history ECG enzyme and autopsy findings according to the WHO criteria [2] The working methods of the Helsinki Register have been published previously [2 2]

In all 1 224 patients under the age of 66 years who suffered an attack of AIHD within the period July 1 1970 to June 30 1971 in Helsinki were registered Of these patients 728 survived the first 28 days During the 5 years after the acute phase 219 patients died 177 of them because of ischemic heart disease (IHD) (a new AMI an SCD or chronic IHD with no other diagnosis) Those 42 patients whose cause of death was other than IHD were excluded from the series Data of deaths were obtained from the Helsinki Coronary Register if the patients had died from AIHD under the age of 65 years and from the Death Cause Register of the Central Office of Statistics in other cases The follow up of the series is complete for the cause of death and the 5 year survival with an accuracy of 1 day There were no discharge ECG s available for 45 patients (6 5 per cent of the 686 patients) and for this reason the P wave analysis is based on a series of 641 patients

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Fig 1 A through C The principles of the P wave measurements. *A (left panel)* The PTF is measured by counting the duration times the amplitude of the negative portion of the P wave *B (center panel)* The PTFA is declared abnormal if the terminal P wave is negative in Lead III and isoelectric (as in the figure) or negative in Lead II *C (right panel)* the duration of the P wave is measured in Leads I II III aV aV$_L$ aV and declared abnormal if its duration is ≥0 12 sec

The total series consists of various subgroups according to the size and site of the recent lesion the presence or absence of earlier myocardial infarction the spectrum of the clinical and radio logical findings etc Due to the limited size of the series comparisons of the P wave findings were not carried out between the subgroups

The last ECG of the patient before his discharge from hospital taken at least 8 days and usually 10 to 14 days after the onset of pain was used for the analysis of the P wave morphology Also an ECG with a normal P wave morphology taken 4 to 7 days after the onset of symptoms was accepted if the patient had no later ECG s The PTF was also measured in all ECG s taken during the first five days in hospital and the maximal PTF during that period was also included in the analysis There was an ECG taken 14 to 21 days after the onset of pain for 406 patients and the PTF was also measured from that ECG and included in the analysis

The ECG s were ordinary 12 lead ECG s and the paper speed was 50 mm /sec The parameters recorded from the discharge ECG were the P terminal force (PTF) the frontal axis of the P wave (PTFA) the duration of the P wave and atrial fibrillation All measurements were carried out by the same investigator (S P) without knowledge of the ultimate prognosis of the patient

The PTF was determined from the duration and amplitude of the terminal deflection of the P wave in Lead V_1 in a way described by Morris and associates in 1964 [6] (Fig 1) The PTF was declared abnormal if the width × the depth of the negative portion was –0 03 mm sec or more negative

The PTFA was determined qualitatively using Leads II and III as originally described by Gooch and colleagues [5] and by Siltanen [12] Cases in which the terminal portion of the P wave 30 msec short of its termination was –30 degrees or more nega tive were classified as having an abnormal axis [4] In other cases it was considered as normal (Fig 1)

The P uaɪe duration was considered abnormal if it was 0 12 sec or more in some of the Leads I II III aV_L aV_R aV_F In other cases it was declared normal (Fig 1)

The statistical evaluations were made by χ^2 test and by Odds ratio based on the Mantel Haenszel test [23] [24] The Odds ratio was used to describe the risk of death of the exposed group (e g., the group with an abnormal PTF) as compared to the nonexposed group (the group with a normal PTF) when the effect of age was standardized Thus the value 1 of Odds ratio means that the risk of death is equal in both groups and figures more positive than 1 tell how manyfold the risk of the exposed group is as compared to the nonexposed group

Results

Of the 631 patients who were in sinus rhythm in the discharge ECG 69 had an abnormal PTF (–0 03 mm sec or more negative) In four of the 631 cases it was not possible to measure the size of the PTF Only 46 4 per cent of the patients with an abnormal PTF survived 5 years as compared to 79 6 per cent of those with a normal PTF ($p < 0\ 001$) (Fig 2) The use of the limit of –0 04 mm sec for abnormality did not strengthen the relationship between the PTF and survival 48 7 per cent of 39 patients with a PTF –0 04 mm sec

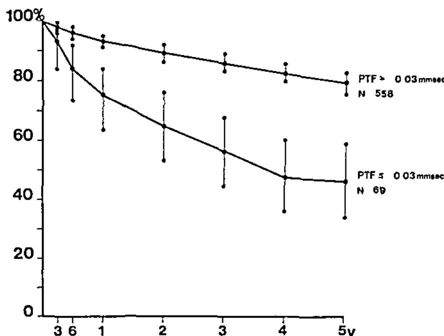


Fig 2 The cumulative 5 year survival percentages with 95 per cent confidence intervals and the PTF in the discharge ECG

or more negative survived 5 years as compared to 77 7 per cent of 588 patients with a less negative PTF No one of the four patients with a PTF −0 06 mm sec or more negative survived (Table I) The 5 year survival curve of 69 patients with an abnormal PTF had an abrupt fall during the first year especially during the first six months whereas the survival curve of the patients with a normal PTF was linear (Fig 2) The Odds ratio which describes the risk of death when the effect of age is standardized was 4 1 (Fig 3)

The PTF was abnormal in at least one of the ECG s recorded during the first five days in hospital in 154 or 598 (25 8 per cent) patients Of the patients with an abnormal PTF during the first five days 59 7 per cent survived 5 years while 81 5 per cent of the patients who had a normal PTF survived The Odds ratio was 2 9 (Fig 3)

There was an ECG taken for 406 patients 14 to 21 days after the onset of pain The PTF was abnormal in 46 cases 45 7 per cent of which survived as compared to the 78 2 per cent survival rate of the 360 patients with a normal PTF The Odds ratio was 4 2 (Fig 3)

Fifteen patients had the PTFA −30 degrees or more negative and seven (46 4 per cent) of them survived 5 years The survival percentage of the patients with a normal axis was 77 9 per cent (Fig 4) The Odds ratio was 4 7 (Fig 5) Two patients had both the abnormal PTF and the abnormal PTFA

The duration of the P wave showed no relationship to the 5 year survival Of the 14 patients with the P wave $\geq$ 0 12 sec 10 (71 4 per cent) survived as compared to 76 0 per cent survival for the patients with normal P wave duration ($p > 0\ 10$) (Fig 4)

Five of the ten patients who had atrial fibrillation died whereas 75 8 per cent of the patients with sinus rhythm survived (Fig 4) The Odds ratio was 2 7 (Fig 5)

Discussion

The presence of atrial fibrillation abnormal PTF, or abnormal PTFA in the discharge ECG turned out to be related to a low 5 year survival rate after infarction The reliability of this observation probably is good because the study population is large and unselective and its follow up is complete [27] the proportion of missing data of ECG is low and the reading of ECGs was carried out by the same investigator The ECG parameters included in the study were easy to classify and the good reproducibility of the variables have been shown previously [10, 12, 28] The relationship between the increased mortality rate and the abnormal P wave morphology persisted even after controlling the effect of age Also in a

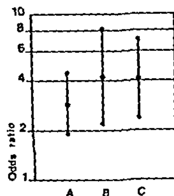


Fig 3 The Odds ratios with 95 per cent confidence intervals for the PTF s measured *A* from the ECG taken 1 to 5 days after the onset of pain, *B* from the discharge ECG *C* from the ECG taken 14 to 21 days after the onset of pain

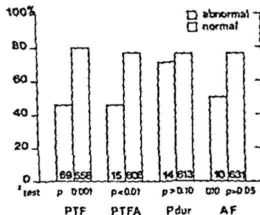


Fig 4 The 5-year survival percentages with 95 per cent confidence intervals as regards the PTF PTFA P wave duration and atrial fibrillation in the discharge ECG

multiple discriminant analysis (not included in the present study) of 11 independent variables for 5 year mortality e g the transmurality of infarction and occurence of previous infarctions the PTF had the strongest discriminant power [29]

The association observed in this study between the abnormal PTF in the discharge ECG and the decreased 5 year survival rate agrees with the observation in a previous study where the predischarge PTF was the best discriminator of the four year mortality rate in the discriminant analysis, and exceeded for example the physical working capacity [7] It has been shown to correlate well during the acute phase of MI with the pulmonary arterial diastolic or wedge pressure which reflect the left ventricular filling pressure [4, 5] It changes rapidly in concordance with the pulmonary artery wedge pressure[1] and with other evidence

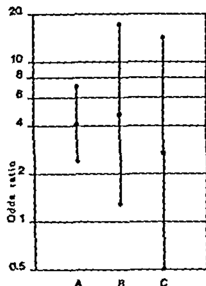


Fig 5 The Odds ratios with 95 per cent confidence intervals for the PTF PTFA and atrial fibrillation in the discharge ECG

of the left ventricular failure based on the chest x rays or clinical examinations [16, 30, 31, 33] In patients with a chronic IHD, mainly an old MI the PTF correlates well with the left ventricular end diastolic pressure (LVEDP) and left ventricular ejection fraction [25] Even a slightly negative PTF seems to indicate an impaired left ventricular function for in a series of 365 subjects without any evidence of IHD it never was −0 03 mm.sec or more negative and only in 1 per cent was it more negative than −0 02 mm.sec but often slightly negative in patients with coronary heart disease and a normal QRST pattern in the ECG [32] Also the changes in PTF and LVEDP during physical exercise present a significant positive mutual correlation in patients with coronary artery disease [33] A depletion of norepinephrine from right atrial tissue as a sign of atrial or atrial and ventricular myocardial failure is usually associated with abnormal PTF and/or PTFA [2] These observations are all in accordance with the generally accepted conception that abnormal PTF is produced by hemodynamical overload of the left atrium [10, 30, 31, 33]

The exact mechanism causing an abnormal PTF in Lead V_1, that is the posterior rotation of the P wave vector in the horizontal plane is not clear It may be due to acute distention of the left atrium which usually occurs in a posterior direction in left ventricular failure [13, 24] PTF has been found also to have some correlation with x ray

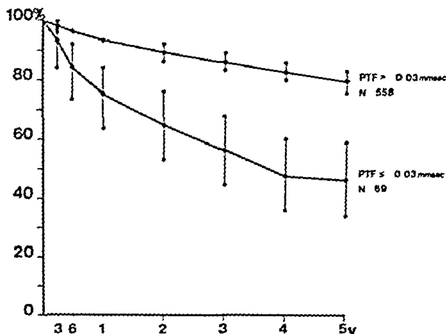


Fig 2 The cumulative 5-year survival percentages with 95 per cent confidence intervals and the PTF in the discharge ECG

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etiological factors do not usually exist in that stage The increased mortality rate during the long term follow up although not statistically quite significant in this study is to be explained probably both by the association of atrial fibrillation with more severe infarction and by its own effect namely by its lowering effect on the cardiac output which may be crucial to the patient with a marginal left ventricular function

All these factors—PTF PTFA and atrial fibrillation—most likely represent the hemodynamic overload in the left atrium due to left ventricular failure and this explains their association with the low 5 year survival rate These variables of the P wave morphology are easy to read in an ordinary ECG and can thus be used for differentiating patients who are in a greater risk to die after the acute phase of myocardial infarction

Summary

The discharge ECG s of 641 patients with acute myocardial infarction (AMI) (WHO categories "definite and possible AMI) were studied to assess the prognostic value of P wave morphology as an index of left ventricular dysfunction Of 69 patients with abnormal P terminal force (PTF) i e −0 03 mm.sec or more negative 53 6 per cent died within the next 5 years of ischemic heart disease compared with 20 4 per cent of 558 patients with normal PTF The Odds ratio (age corrected risk to die Mantel Haenszel test) was 4 1 (95 per cent confidence limits 2 4 to 7 0) The mortality curve of patients with normal PTF was linear whereas there was an abrupt rise in mortality rate during the first six months if PTF was abnormal Of a group of 15 patients with the frontal axis of the terminal P wave −30 degrees or more negative 8 died (Odds ratio 4 7 1 3 to 17 1) Ten patients had atrial fibrillation and five of them died (Odds ratio 2 0 5 to 12 9) In 14 cases the duration of the P wave in Lead II was 0 12 sec but it showed no relationship to mortality ($p > 0 10$)

The significance of the P wave morphology on the discharge ECG to long term survival after MI has been demonstrated These simple ECG variables related to left ventricular failure can easily be put to clinical use to differentiate MI patients who are in greater risk of dying during the chronic phase

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Experimental and laboratory reports

Effect of somatic nerve stimulation on coronary blood flow in anesthetized dogs

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Stimulation of somatic afferent fibers elicits cardiovascular responses in several vascular beds the direction and magnitude of the change being dependent upon the activating stimulus or the frequency and intensity of nerve stimulation[1,2] The influence of activation of somatic afferent fibers on the coronary circulation has not been described although changes in myocardial contractility[4] heart rate[5] and cardiac output[3] have been shown to occur during high frequency high intensity stimulation of somatic nerves

Numerous studies over the past 15 years have been concerned with neural control of the coronary circulation[6] Stimulation of the stellate ganglion[7,8] activation of baroreceptors[9,10] or chemoreceptors[11] and observations of coronary blood flow in chronically instrumented conscious dogs[1] have suggested that in general the autonomic nervous system can be shown to directly influence coronary vascular resistance under certain conditions As the integrated cardiovascular response to activation of somatic and cardiovascular afferent fibers may be different[3] it was decided to study the effect of somatic nerve stimulation on coronary blood flow The mechanism for the observed changes in coronary blood flow was determined by using various combinations of nerve stimulation cardiac pacing and administration of propranolol

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Methods

Experiments were done on mongrel dogs (18 to 22 kilograms) initially anesthetized with an intravenous injection of α chloralose (75 mg /Kg) and urethane (500 mg /Kg) A stable level of anesthesia was maintained by an intravenous infusion of α chloralose and urethane (20 to 40 mg /Kg hr each) using an infusion pump (Harvard Apparatus Co) Dogs were intubated and ventilated (Harvard pump) with air at a rate and depth of ventilation to maintain end tidal CO_2 concentration at approximately 5 per cent (Beckman LB 1 gas analyzer) Rectal temperature was maintained at 38 ± 1° C by a heating pad controlled by a temperature controller (Yellow Springs Instruments Co)

Arterial pressure was measured from the thoracic aorta via a cannulated femoral artery connected to a pressure transducer (Statham P23Dc) and displayed with other recorded variables on a Grass model 7 polygraph Both mean and pulsatile pressure were monitored simultaneously the mean pressure being obtained by electronic averaging of the pulsatile output from the Grass amplifier Heart rate was obtained by using the arterial pulse to trigger a tachograph (Grass 7P4)

Left circumflex coronary artery blood flow (CBF) was measured electromagnetically using a Biotronex flowmeter (BL 610) The thorax was opened on the left side and the pericardium was opened and sutured to the chest wall to form a pericardial cradle for the heart The circumflex branch of the left coronary artery was carefully isolated to provide sufficient area for the flow probe and a cotton snare was placed distally to the probe to be used to temporarily occlude the artery for mechanical determination of zero flow

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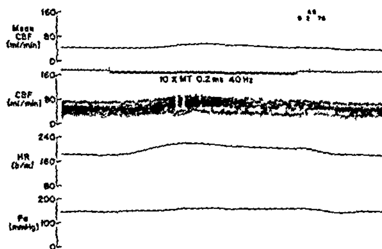


Fig 1 Representative tracing of the effect of stimulation of the tibial nerve on coronary blood flow *(CBF)* through the circumflex artery heart rate *(HR)* and mean arterial pressure *(Pa)* The total duration of the stimulation as indicated by the time marker was 60 sec *MT* = motor threshold (see text for definition)

The flow probe a narrow width model with an internal diameter of 2 0 mm (Biotronex) was calibrated previously *in vitro* with dog blood and in one experiment *in vivo* with the probe on the internal thoracic artery Both calibrations were identical and linear over the range of flows recorded in this study Mechanical determination of zero flow was tested frequently to insure that the baseline was stable throughout the experiment Both mean and pulsatile circumflex flow were recorded simultaneously using a circuit as described for arterial pressure

The intact tibial nerve was stimulated with bipolar platinum alloy sleeve electrodes using a stimulus isolation unit (Grass SIU 5) with 0 2 msec rectangular pulses from a Grass S4 stimulator at frequencies of 4 to 100 Hz and at intensities ranging from 2 to 20 times the motor threshold Motor threshold was determined by gradually increasing the intensity of a 4 Hz stimulus until muscle twitches were just observable Stimulation of the tibial nerve was done for 60 sec and the interval between successive stimulations was 15 minutes

In eight experiments the effect of changes in heart rate on CBF was determined with and without accompanying stimulation of the tibial nerve For these experiments the heart was paced by inserting two pin electrodes into the wall of the left atrium and providing a pacing stimulus of 2 msec duration at twice the pacing threshold (Grass SD5) Without stimulation of the tibial nerve the heart was paced for 60 sec at a rate similar to that recorded during the previous stimulation of the tibial nerve combined with tibial nerve stimulation the heart was paced at a rate slightly higher than that seen during the previous nerve stimulation beginning 15 sec before and continuing throughout the 60 sec stimulation of the tibial nerve Propranolol (1 0 mg/Kg intravenously) was used in seven experiments to investigate the role of cardiac β adrenergic stimulation on the responses obtained during stimulation of the tibial nerve

The recorded variables were analyzed at 5 sec intervals starting 15 sec before and continuing for 30 sec after an experimental maneuver At least two responses to a given experimental procedure were obtained and used to determine an average response for that animal Mean circumflex coronary vascular resistance (CVR) was calculated from the values of mean CBF and mean arterial pressure at each time interval Venous pressure was assumed to be constant and negligible under these conditions In eight experiments late diastolic vascular resistance was calculated from tracings of pulsatile pressure and flow Several cardiac cycles were used to obtain an average value for the measured variables at the appropriate time intervals The changes in CBF CVR, heart rate and mean arterial pressure were expressed as the mean ± standard error (S E) difference from the control Where possible experimental procedures were randomized between animals The data were analyzed using Duncan s New Multiple Range Test [9] A probability of $P < 0.05$ was accepted as the minimal level of significance

Results

Effects of tibial nerve stimulation Although in preliminary experiments various combinations of stimulation frequencies and intensities were studied it was found that the stimulation parameters which gave the most consistent response over a 60 sec period were a frequency of 40 Hz and an intensity of 10 times motor threshold Lower intensities and frequencies tended to yield small biphasic responses and higher intensities (up to 20 times motor threshold) produced hemodynamic responses which were not significantly different from the 10 times motor threshold response although marked respiratory movements were often noted at the higher intensities Therefore it was decided that the response to a stimulus at 40 Hz 10 times motor threshold would be studied in detail

A representative tracing of the response obtained during a 60 sec stimulation of the tibial nerve is shown in Fig 1 Heart rate and arterial blood pressure began to increase within 5 sec of the onset of stimulation while CBF was just beginning to increase after 10 to 15 sec By 30 sec all three recorded variables had reached a peak The mean responses obtained in 11 experiments during 60 sec stimulation of the tibial nerve at 10 times motor threshold 40 Hz are shown in Fig 2 The data are plotted as the mean change from the pre stimulus control Changes in CBF tended to parallel the changes in heart rate

Fig 3 shows the average change in calculated mean CVR during the 60 sec stimulation period In eight experiments late diastolic CVR was calculated from the pulsatile pressure and flow tracings to provide an estimate of CVR which was independent of passive factors which influence CVR As noted by Feigl [9] changes in late diastolic CVR were found to follow the same pattern as those for changes in mean CVR therefore only changes in mean CVR were examined in subsequent studies

Effect of cardiac pacing To determine the mechanism for the change in coronary blood flow during stimulation of the tibial nerve in eight experiments the heart was paced at a rate which simulated that seen during nerve stimulation A step increase in heart rate resulted in a gradual increase in mean CBF which reached a maximum at 20 to 30 sec and was maintained for the rest of the pacing period There was no change or a slight increase in mean arterial pressure during pacing

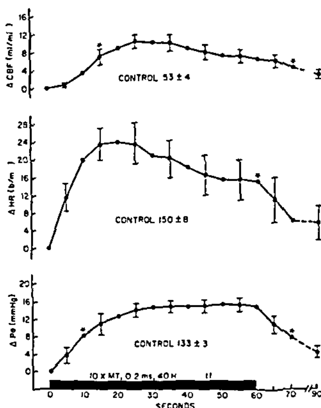


Fig 2 Effect of stimulation of the tibial nerve on mean coronary blood flow through the circumflex artery heart rate and mean arterial pressure Data are expressed as mean (±S E) change from pre-stimulus control (S E bars shown at 10 sec intervals only) *Points between the two asterisks* are significantly different ($P < 0.05$) from zero

Since CBF reached a peak and mean CVR was significantly decreased at 30 sec during nerve stimulation this time period was selected to be compared with results obtained during pacing Fig 4 shows the average responses at the 30 sec mark of the experimental procedure During pacing the increase in CBF was significantly less (about 40 per cent) than that seen during stimulation of the tibial nerve while mean CVR was significantly reduced and arterial pressure remained constant In eight animals pacing was done during stimulation of the tibial nerve so that the heart rate remained constant during nerve stimulation Table I shows that under these conditions CBF increased significantly along with a significant increase in arterial pressure CVR tended to decrease further but the change was not significantly different from the CVR calculated during pacing alone

Effect of propranolol In seven of the 11 experiments stimulation of the tibial nerve was

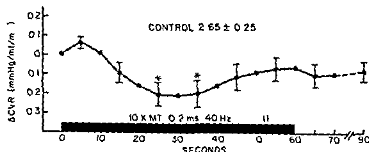


Fig 3 Fffect of stimulation of the tibial nerve on mean coronary vascular resistance *(CVR)* of the circumflex vascular bed CVR was calculated from values of mean artenal pre^sure and mean coronary blood flow The format of the figure is the same as that of *Fig 2*

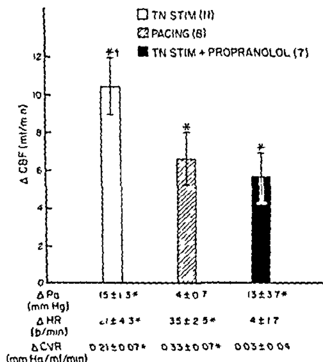


Fig 4 Summary of effect of stimulation of the tibial nerve *(TN)* cardiac pacing or nerve stimulation plus propranolol on mean coronary blood flow mean arterial pressure heart rate and mean coronary vascular resistance Values are mean (±S E) change from control after 30 sec of nerve stimulation or pacing Numbers in parentheses are numbers of animals per group I < 0 0ɔ compared to zero †P < 0 0ɔ compared to TN stim + propranolol or pacing Abbreviations as in previous figures

repeated before and 5 minutes after administra tion of propranolol (1 0 mg /Kg intravenously) This dose of propranolol was sufficient to completely block the cardiac and peripheral effects of a test dose of isoproterenol (0 1 µg/Kg intravenously) As seen in Fig 4 stimulation of the tibial nerve in the presence of β adrenergic blockade resulted in an increase in CBF which was significantly less (approximately 50 per cent) than that seen before propranolol The increase in

Table I Changes in coronary blood flow, heart rate mean arterial pressure and mean coronary vascular resistance during cardiac pacing or pacing plus stimulation of the tibial nerve (TN)

	ΔCBF *ml /min*	ΔHR *b /min*	ΔPa *mm Hg*	ΔCVR *mm Hg/ ml min*
Pacing†	51 ± 14	30 ± 32	1 ± 05	−029 ± 009
Pacing + TN‡	136 ± 17	30 ± 32	16 ± 27	−040 ± 016

CBF = coronary blood flow HR = heart rate Pa = mean arterial pressure CVR = mean coronary vascular resistance
n = 8 I < 0 0ɔ when compared to zero
All values are mean (±S E) change from control
†Values after 15 sec of pacing just prior to stimulat on of the TN (10 × MT 0 2 msec 40 Hz)
‡Values after 30 sec of nerve stimulation + pacing

CBF occurred along with a significant increase in mean arterial pressure and with no change in heart rate or mean CVR

Discussion

Stimulation of somatic afferent fibers has been shown to elicit cardiovascular responses in many vascular beds the magnitude and direction of the response depending upon the stimulus frequency and intensity [1] The response presumably is depen dent upon the type of afferent fibers activated In the present study stimulation of the intact tibial nerve at 10 × MT 40 Hz resulted in a significant increase in CBF which could be attributed to an increase in perfusion pressure and a decrease in CVR Previous studies in dogs have shown that the intensity and stimulation of the tibial nerve used in this study activated afferent fibers belonging to groups I to III with possible inclu sion of some in group IV [1] It is possible indeed probable that some of the effect originated from receptors activated by contracting skeletal mus

cle since the intact nerve was stimulated and the animals were not paralyzed[15]

The increase in CBF is what would be expected under the conditions of increased sympathetic nervous system activity resulting in increased heart rate and arterial pressure However as pointed out by Feigl[9] the exact mechanism for a change in CBF must be considered in the light of the many factors which can influence CBF—i e perfusion pressure myocardial systolic compression and metabolic and neurohumoral control of CVR

In the present study an attempt was made to control or account for the contribution of these various factors in determining the mechanism for the change in CBF during stimulation of the tibial nerve The peak mean flow and the factors influencing it were investigated since this period represented a reasonably stable period for all the recorded variables In several experiments the effect of systolic compression was examined by calculating late diastolic CVR As changes in late diastolic CVR and mean CVR were found to be similar in agreement with previous findings[9] in subsequent studies only the mean CVR was used

Since the change in CBF produced by stimulation of a somatic nerve seemed to follow fairly closely the change in heart rate it was decided to investigate the effects on CBF of a similar change in heart rate due to electrical pacing of the heart A step change in heart rate to a level actually somewhat higher than that seen during pacing was due entirely to a decrease in CVR since perfusion pressure (i e mean arterial pressure) remained constant Combining nerve stimulation with pacing produced a further increase in CBF which could be attributed to the increase in mean arterial pressure Although calculated CVR was not significantly different from the condition of pacing alone there was a tendency for CVR to decrease further which may reflect the effects of increased afterload and increased myocardial contractility during somatic nerve stimulation

The role of increased perfusion pressure in producing the changes in CBF observed during somatic nerve stimulation was investigated by eliminating the increases in heart rate and contractility elicited by increased cardiac sympathetic activity While it is difficult to produce complete β adrenergic blockade the dose of propranolol used did completely block the chronotropic effects of somatic nerve stimulation while the increase in arterial pressure was similar to that seen before administration of propranolol Under these conditions CBF increased to about 50 per cent of that seen during stimulation of the tibial nerve before administration of propranolol the basis for the increase in flow being an increase in perfusion pressure with no change in CVR

The constant mean CVR during stimulation of the tibial nerve in the presence of β adrenergic blockade is interesting from the standpoint of neural control of CVR Arterial baroreceptor reflexes have been shown to directly increase CVR under these conditions as a result of the unmasking of α adrenergic vasoconstriction[9, 10] On the other hand hypoxic hypercapnic activation of carotid body chemoreceptors has been shown to have no significant effect on CVR the increase in CBF in this preparation being accounted for by the increase in perfusion pressure[16]

It is possible that the failure of somatic nerve stimulation to produce neurally mediated changes in CVR in this study reflects to some extent the partial denervation which probably occurs when using the cuff type electromagnetic flow probe on the circumflex artery[17] Using a similar preparation Feigl[9] showed a small increase (14 per cent) in CVR 30 sec after occlusion of the common carotid arteries in the presence of β adrenergic blockage, however based upon the cardiovascular responses it is reasonable to assume that the degree of activation of the sympathetic nervous system was far greater in the latter study than in the present study In addition Mohrman and Feigl[18] have recently demonstrated a competition between sympathetic vasoconstriction and metabolic vasodilation in the coronary circulation In their study reflex activation of the sympathetic nervous system or intracoronary administration of norepinephrine resulted in a greater coronary vasodilation after α adrenergic blockade It is possible in the present studies that metabolic vasodilation in response to increased afterload was in competition with sympathetic vasoconstrictor effects thus leading to no observable change in resistance in the presence of β adrenergic blockade

Similarly the results of this study agree with those reported in humans by Mudge and associates[19] in which an increase in coronary sinus

flow at a controlled heart rate was seen during a 50 sec. cold pressor test. The change in coronary sinus flow was accompanied by a 15 mm Hg rise in mean arterial pressure and no change in calculated CVR. In patients with coronary artery disease the same test resulted in an increase in calculated CVR which was attributed to an increase in neural tone to coronary vessels which were already maximally dilated in response to the disease process. Therefore under conditions of controlled heart rate the failure to detect neurally mediated coronary vasoconstriction in normal patients[14] or anesthetized dogs during activation of somatosympathetic reflexes could be explained by the fact that local vasodilation in response to the increased myocardial contractility and increased afterload may just offset the increase in neural tone.

Summary

Left circumflex coronary blood flow was increased significantly (20 per cent) during stimulation of somatic afferent fibers. The change in CBF was associated with significant increases in heart rate and arterial pressure and a significant decrease in coronary vascular resistance. Controlling heart rate or preventing cardiac β adrenergic effects with propranolol during somatic nerve stimulation resulted in increases in CBF and arterial pressure with no change in coronary resistance. These results indicate that stimulation of a somatic nerve elicited an increase in CBF which could be explained on the basis of an increase in perfusion pressure plus a decrease in CVR resulting from the increased metabolic demand secondary to the increase in heart rate. There was no evidence of a significant neural component directly affecting CVR even in the presence of β adrenergic blockade.

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A quantitative study of parameters obtained by a bedside mechanographic method in valvular lesions

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Recent developments in mechanographic methods using high fidelity instruments have shown that parameters obtained by non invasive techniques may be fair indices of invasive physiological measurements that are generally accepted as satisfactory indices of the myocardial condition[1] The time differentiation of the arterial pulse and of the apical impulse [4] has increased the usefulness of mechanographic methods High fidelity however implies usually complex expensive bulky instrumentation and time consuming methods all of which reduce the practical merits of non invasiveness

In 1970 a simple bedside method was reported for recording the time derivative of the carotid pulse and the apical impulse on a common one channel recorder[6]

Mechanographic parameters have been employed extensively in order to assess myocardial function using either carotid impulse recordings[7] or the apex cardiogram These parameters however may be influenced by valvular lesions of the heart Such influence might be an aid in diagnosing the valvular lesion but it might also obscure the concomitant presence of myocardial disease

The above mentioned method has proved fairly sensitive in detecting deviations of the myocardial function from normal as in coronary artery disease and in thyrotoxicosis[11]

The purpose of this paper is to evaluate the effect of valvular diseases on parameters obtained on a one channel recording by the bedside technique mentioned above and to estimate the diagnostic efficiency of these parameters

Material and method

The transducer used for this work has been described in detail elsewhere Briefly it consists of a coil and a small magnet separated by an air filled balloon The coil is fixed with a plate the rim of which is pressed on the point of maximal pulsation manually The magnet at the center of the plate is moved by the pulsation in respect to its surrounding rim i e against the coil A potential difference is thus created in the coil which is proportional to the time derivative of the movement The coil is connected with the two electrodes of a bipolar lead of a common ECG recorder through a variable resistance in series The same ECG electrodes are placed on two sites of the patient in order to record his ECG on the same ECG channel

One hundred thirty seven patients with aortic or mitral valve diseases form the group of patients in this paper Cases with more than one valve disease were excluded The diagnosis was established by cardiac catheterization or in some obvious cases on clinical grounds The patients were divided into six groups according to their valvular lesions (Table I) There were 34 cases with mitral stenosis (MS) 23 with mitral regurgitation (MR) 16 with double mitral lesion (MRS)

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Table I Mean values ± SEM of the parameters examined

Parameter	Normal	MS	MR	MRS	AS	AR	ARS
No of cases	103	34	23	16	28	22	14
No in SR	103	21	18	6	27	21	13
Age	34.49	43.91	49.74	50.75	39.79	45.54	48.00
(years)	±1.56	±2.34	±3.94	±3.77	±3.22	±2.71	±3.28
R R	782.35	762.54	799.30	888.87	842.72	817.89	749.14
(ms)	±15.33	±29.77	±39.99	±40.34	±31.02	±39.28	±33.27
Q-dC	110.99	113.03	111.27	123.08	101.17	111.43	104.58
(ms.)	±1.64	±4.21	±4.93	±6.21	±3.46	±4.89	±3.56
dC -dC	262.13	250.47	232.17	245.61	277.32	269.97	298.08
(ms)	±1.95	±5.36	±7.64	±11.39	±6.5[illegible]	±8.47	±13.84
(Q-dC)/(dC -dC)	42.53	45.67	49.04	51.46	36.96	41.71	36.17
(%)	±0.85	±2.09	±2.80	±3.63	±1.43	±2.16	±2.65
1000a/(b + e)	44.20	47.30	99.59	52.33	196.17	182.09	159.15
	±6.07	±12.87	±20.76	±24.38	±28.82	±36.58	±41.23
1000b/(b + e)	599.32	608.91	539.09	538.12	543.29	522.77	511.57
	±11.11	±20.83	±22.76	±26.61	±27.05	±39.55	±26.98
1000c/(b + e)	108.60	263.59	80.65	147.08	57.87	104.09	36.17
	±10.13	±33.59	±24.15	±80.79	±16.15	±31.99	±12.23
1000f/(b + e)	53.01	49.15	170.43	139.75	84.64	107.86	130.79
	±6.54	±16.07	±32.89	±33.08	±20.09	±25.31	±57.77
1000(a + f)/(b + e)	97.28	77.82	244.04	1[illegible]9.37	251.39	281.68	278.57
	±8.99	±19.85	±39.79	±35.70	±35.02	±46.90	±76.84

28 with aortic stenosis (AS) 22 with aortic regurgitation (AR) and 14 with double aortic lesion (ARS) Thirty one cases had atrial fibrillation (AF) Table I shows the basic features in each group No discrimination was made on the basis of the degree of valvular lesion on the presence of heart failure or on drug administration

The findings from these patients were compared with those obtained from a group of 103 subjects without heart disease The findings on the normal group have been described in detail elsewhere and will be mentioned briefly here The carotid pulse derivative (dC/dt) was recorded together with the ECG of the patient (Fig 1) The beginning of the QRS (point Q) the rapid upstroke of the pulse tracing (dC) as suggested by Nandi and Spodick [3] and the nadir of the pulse tracing (dC) were clearly seen The intervals Q-dC and dC -dC were measured representing a rough index of the preejection (PEP) and ejection period (EP) respectively Similarly the ratio (Q dC)/(dC dC) was calculated and considered as an index of the PEP/EP ratio

The dA/dt was recorded with the patient in a left lateral position in held mid expiration without his ECG Recordings were made either on a photographic Sanborn Twin Viso simultaneously with the phonocardiogram at a 75 mm /sec paper speed or on a Hewlett Packard direct writing one channel ECG recorder at a 50 mm /sec paper speed In 20 subjects of the normal group dA/dt and dC/dt were recorded both by electronically differentiating the apex cardiogram and the carotid pulse and by the method mentioned above on an Electronics-for Medicine polygraph The phonocardiogram was also recorded simultaneously

On dA/dt six main waves could possibly be seen (Fig 2) named after the first six letters of the Latin alphabet The amplitude of the waves a b c e and f was measured from the isoelectric line recorded with the transducer left apart from the patient before and at the end of pulse recording The positive a wave corresponding to the rate of rise of the a wave on an ordinary apex cardiogram was absent in the AF cases The positive b wave corresponded to the velocity of the ascending limb of the apex cardiogram (contraction) The negative c wave was a continuation of the descending limb of the b wave The positive d wave sometimes preceded the negative e wave and has been considered of no clinical importance [4] The e wave corresponded to the rate of fall of the descending limb of the apex cardiogram (relaxation) *Finally the positive f wave corresponded to* the rapid filling phase of the heart cycle Only the

b and e waves were present in all cases The a b c f wave amplitudes and the sum a + f were expressed as a ratio over the sum of b + e waves of the same cardiac cycle and the ratios a/(b + e) b/(b + e) f/(b + e) and (a + f)/(b + e) were multiplied by 1 000 Both for the dC/dt and the dA/dt measurements five to seven cycles were averaged

The parameters from dC/dt and from dA/dt in the normal group were plotted against the subjects age and the R R interval preceding the cycle was measured In the diagrams of a/(b + e) f/(b + e) and (a + f)/(b + e) against age and in the diagram of c/(b + e) against R R interval the ordinate values might range from zero to an upper limit which seemed to be a function of age or of R R interval so that the scatter diagram covered a more or less triangular area In such diagrams a line representing the upper normal limits would be more informative than the mean regression line and its standard deviation In order to obtain an upper normal line excluding above it approximately 10 per cent of the population the range of the abscissa was divided into equal intervals the number of which was twice the 10 per cent of population (i e 20 intervals in the group of 103 subjects) The highest value in each interval was then noted and the regression line of these values was calculated The mean regression line of each parameter against age or R R interval in the normal group was considered as the expected value The mean difference between observed and expected values of all parameters examined was calculated in each one of the six valvular lesion groups applying the paired t test The ratio a/(b + e) was calculated only for the cases in sinus rhythm (SR)

In order to calculate the efficiency of each parameter in diagnosing the valvular lesion the following method was applied For the parameters forming in the normal group a triangular scatter diagram with age or R R interval the 90 per cent upper normal limit was used to separate positive (above the line) from negative (below the line) results For the parameters forming in the normal group a straight line scatter diagram a line 1 645 × standard deviation above or below the mean regression line was considered as the normal limit of the parameter examined Between the upper and lower normal limits thus calculated approximately 90 per cent of the normal population were expected to lie The

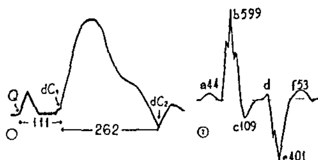


Fig 1 Schematic representation of dC/dt Figures represent mean intervals of the normal group in msec

Fig 2 Schematic representation of dA/dt Figures represent mean amplitude of corresponding waves as described in the text

Table II

Result	Valve lesion	Normal	Total
Positive	W	X	W + X
Negative	Y	Z	Y + Z
Total	W + Y	X + Z	W + X + Y + Z

results were positive beyond the normal limits and within normal limits the results were negative The number (W X Y Z) of positive and negative results in the normal and in the valvular lesion groups were then counted and tabulated according to Table II Sensitivity specificity predictive value and efficiency of the parameters were calculated applying the following formulas[1] obtained from Table II

Sensitivity = W/(W + Y)
Specificity = Z/(X + Z)
Predictive value = W/(W + X)
Efficiency = (W + Z)/(W + X + Y + Z)

Findings

A Normal group An example of the dC/dt and dA/dt in the normal group is seen in Fig 3

The mean values of the parameters examined are presented in Table I The parameters a/(b + e) f/(b + e) and (a + f)/(b + e) were significantly correlated with age while the parameters Q dC dC_1 dC ($Q\ dC_1$)/(dC dC) b/(b + e) and c/(b + e) were significantly correlated with the R R interval Table III shows the regression equations of these parameters as well as the normal limits as defined in the Method section The interval from the second sound to dC_2 was 13 13 ± 2 18 msec Point dC preceded always the dicrotic notch by 25 58 ± 2 79 msec

Table III Regression equations of the parameters examined (y) as a function of age (A) or R R interval (T) and their normal limits within (L) or below (U) which 90 per cent of normal population are expected to be included

y	*Equation*	*P<*	*U*	*L*
Q-dC (ms)	y = 89.08 + 0.028T	0.01		L = y ± 26
dC-dC (ms.)	y = 153.97 + 0.139T	0.001		L = y ± 37
(Q-dC)/(dC-dC)(%)	y = 52.97 – 0.014T	0.001		L = y ± 11
a/(b + e) × 1000	y = 24.27 + 0.58A	0.10	U = 79.80 + 0.43A	
b/(b + e) × 1000	y = 755.95 – 0.201T	0.01		L = y ± 16
c/(b + e) × 1000	y = 255.76 – 0.187T	0.01	U = 511.98 – 0.355T	
f/(b + e) × 1000	y = 116.48 – 1.84A	0.001	U = 259.16 – 3.83A	
(a + f)/(B + e) × 1000	y = 140.75 – 1.26A	0.05	U = 338.96 – 3.40A	

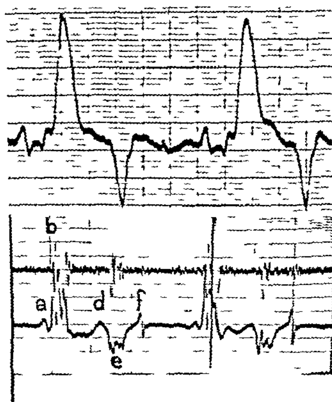


Fig 3 *Upper recording* QRS complex and dC/dt of a normal person (direct writing ECG machine 50 mm/sec paper speed) *Lower tracing* phonocardiogram and dA/dt on a normal child with a very prominent f wave (photographic recording, 75 mm/sec paper speed)

B Valvular lesion groups The mean values of the parameters examined in each valvular group are presented in Table I The mean differences between observed and expected values of all parameters examined may be seen in Table IV

In *mitral stenosis* the dA/dt was not recorded in one case A significant reduction was observed in the dC_1 dC interval and a significant increase in the c/(b + e) ratio Fig 4 shows an example of dA/dt in an MS case

The majority of cases with MS (56 per cent) *had a c/(b + e) ratio higher than the upper* normal limits while only 24 per cent of the cases had a value lower than the mean expected for their R R interval (Fig 5) The sensitivity specificity predictive value and efficiency of c/(b + e) in diagnosing MS from normal are seen in Table V

In *mitral regurgitation* the dC/dt was not satisfactorily recorded in one case A highly significant shortening in the dC_1 dC_2 interval was found associated with a significant increase in the $(Q\text{-}dC_1)/(dC_1\ dC_2)$ ratio (Table IV) Sixty four per cent of the cases had a dC_1 dC_2 value lower than one standard deviation below the expected value for their R R interval and there was only one case with a dC_1 dC_2 value higher than normally expected (Fig 6) Accepting 1.645 × SD below mean expected as the low normal limits the efficiency of this parameter in diagnosing MR from normal is 0.84 (Table V)

Significant changes were also found in dA/dt (Fig 7) Ratios a/(b + e) f/(b + e) and (a + f)/(b + e) were found higher than normal and the b/(b + e) ratio was lower than the expected mean value (Table IV) The majority of cases (70 per cent) had an f/(b + e) ratio well above the ninetieth percentile of the normally expected value for their age and only three cases had a value slightly lower than the mean expected ratio (Fig 8) The diagnostic efficiency of this parameter was 0.87 (Table V) Similarly the (a + f)/(b + e) ratio was found lower than normally expected in 17 per cent of the cases while in 74 per cent this

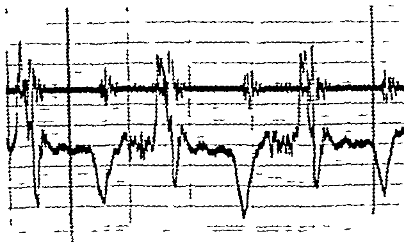


Fig 4 dA/dt and phonocardiogram in a case of mitral stenosis Note diastolic thrill in dA/dt curve.

Table IV Mean differences (±SEM) between observed and expected values with the statistical significances of the mean difference (P<)

Lesion	Q-dC (msec)	dC -dC (msec)	Q-dC / dC -dC	1000a / b + e	1000b / b + e	1000c / b + e	1000f / b + e	1000(a + f) / b + e
MS	+2.73	−11.00	+3.97	+2.00	+10.15	+156.09	+7.69	−9.03
	±3.89	±4.72	±[illegible].15	±13.40	±20.06	±34.41	±14.61	±18.83
	NS	0.05	NS	NS	NS	0.001	NS	NS
MR	+0.19	−3[illegible].00	+7.59	+43.33	−60.56	−77.13	+137.20	+16[illegible].75
	±6.37	±5.55	±2.54	±[illegible]0.24	±23.07	±25.61	±32.17	±39.26
	NS	0.001	0.01	0.05	0.02	NS	0.001	0.001
MRS	+9.61	−31.31	+10.61	+0.63	−3[illegible].75	+8[illegible].27	+114.62	+82.69
	±5.68	±9.48	±3.83	±[illegible]4.31	±108.98	±71.74	±32.78	±35.12
	NS	0.005	0.0[illegible]	NS	S	NS	0.005	0.05
AS	−10.41	+10.[illegible]5	−4.22	+139.96	−40.82	−37.12	+39.54	+161.46
	±3.24	±7.47	±1.60	±28.24	±23.07	±15.26	±20.15	±35.55
	0.00[illegible]	NS	0.0[illegible]	0.001	NS	0.01	0.1	0.001
AR	−0.81	+1.73	+0.57	+132.00	−64.82	−0.09	+74.91	+198.32
	±4.64	±5.78	±2.22	±36.10	±32.32	±34.64	±26.26	±48.06
	NS	NS	NS	0.005	0.05	NS	0.01	0.001
ARS	−5.00	+40.33	−6.00	+107.00	−93.57	−60.92	+10[illegible].43	+19[illegible].50
	±3.69	±12.7[illegible]	±2.40	±41.45	±[illegible]7.61	±12.92	±56.71	±76.02
	NS	0.01	0.05	0.025	0.005	0.001	0.1	0.0[illegible]

ratio had a value above the 90 per cent upper normal limits and its diagnostic efficiency was 0.87 (Table V)

In *double mitral lesion* a significant shortening in the dC -dC interval was noted together with an increase in the (Q-dC)/(dC -dC) ratio The dA/dt showed a significant increase in the f/(b + e) and (a + f)/(b + e) ratios None of the above changes was so marked as in the cases of pure MR On the other hand c/(b + e) tended to be higher than normal as in MS but the change was not significant at the 0.05 level.

The Q-dC, interval was significantly lower than normally expected in *pure aortic stenosis* The sensitivity of this parameter in diagnosing AS was low (only 24 per cent of the cases could have been diagnosed by their presenting a Q-dC, interval shorter than 1.645 × SD msec below the *mean* expected value) This parameter however had a high specificity (0.96) with a diagnostic efficiency of 0.82 (Table V) Concomitantly with the Q-dC shortening *a (Q-dC)/(dC,-dC)* fraction significantly lower than normally expected was noted

Apart from its quantitative changes the dC/dt

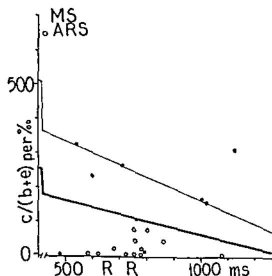


Fig 5 Scatter diagram of c/(b + e) versus R R interval in the cases with mitral stenosis and double aortic lesion *The thick line* represents the average normal (regression line of the least squares) and *the thin line* represents the upper normal limits

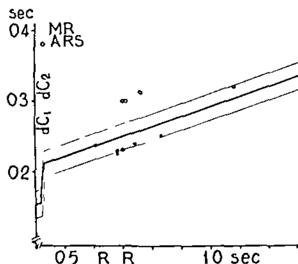


Fig 6 Diagram of dC dC versus R R interval in the cases with mitral regurgitation and double aortic lesion *The thick line* represents the average normal (regression line of the least squares) and the *thin lines* are placed one standard deviation above and below the average normal

had a configuration which was grossly distorted in AS Full sensitivity of the ECG amplifier was needed to record dC/dt in AS and recording of a thrill made its appearance unique (Fig 9)

The most striking effect of AS on dA/dt was a marked increase in the a/(b + e) fraction (Fig 9) In one case the dA/dt was not satisfactorily recorded In one case there was AF In the remaining 26 cases 73 per cent had an a/(b + e)

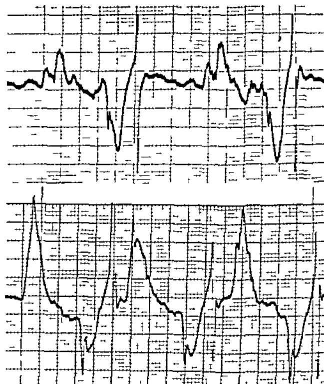


Fig 7 dA/dt in a case of mitral regurgitation in sinus rhythm (*upper tracing*) and of the same case in atrial fibrillation (*lower tracing*)

ratio well above the upper normal limits with only one case (4 per cent) presenting a value below the mean expected value (Fig 10) The efficiency of a/(a + b) in diagnosing AS from normal was 0 85

Although the normal c/(b + e) ratio could have any value from zero to the limits given in Table III in AS this fraction was very close to zero in most cases so that the mean difference between observed and expected value was significantly negative (Table IV)

The f/(b + e) fraction tended to be higher than normally expected ($P < 0\,10$) and the (a + f)/(b + e) ratio was very significantly higher than normal (Table IV)

In *aortic regurgitation* the dC/dt configuration was typically double peaked in all cases (Fig 11) Both diastolic waves i e a/(b + e) f/(b + e) and (a + f)/(b + e) ratios were significantly higher than normally expected (Table IV) The *efficiency of (a + f)/(b + e) in differentiating AR* from normal was 0 84 (Table V) The b/(b + e) ratio was significantly lower than expected (Table IV)

In *double aortic lesion* the dC_1 dC_2 interval was

Table V Diagnostic values of dC/dt and dA/dt parameters

Lesion	*Parameter*	*Sensitivity*	*Specificity*	*Efficiency*	*Pred value*
MS	c/(b + e)	0.5[illegible]	0.89	0.81	0.62
MR	dC-dC	0.41	0.94	0.84	0.60
MR	f/(b + e)	0.73	0.91	0.88	0.64
MR	(a + f)/(b + e)	0.63	0.90	0.87	0.63
AS	Q-dC	0.[illegible]4	0.96	0.82	0.60
AS	a/(b + e)	0.73	0.88	0.85	0.61
AR	(a + f)/(b + e)	0.59	0.90	0.84	0.57
ARS	c/(b + e)	1.00	0.46	0.53	0.20

Using the m n regression line for the separati n between normal and disease

longer than normally expected and the (Q dC_1)/(dC_1 dC) ratio was below normal Sixty seven per cent of the cases had a dC dC_2 interval longer than 1 SD above normally expected (Fig 6) and the diagnostic efficiency of this parameter for ARS was 0 91 (Table V)

Discussion

The parameters examined in this paper seem to cluster fairly close to a mean value in the normal group while they may grossly deviate from normal in disease The diagnostic efficiency of some of the parameters used ranged between 0 81 and 0 91 Thus in spite of the method limitations *the diagnostic efficiency of the method* coupled with its easy bedside applicability might probably render it a useful empirical tool

On the other hand the method used in this work has several technical disadvantages the most important of which are (a) its time constant is finite limited chiefly by the short time constant of the ECG recorder (b) the distance of the magnet from the coil is not absolutely fixed so that changes occurring with the magnet close to the coil (e g during systole) are exaggerated relative to similar changes with the magnet far from the coil (as during diastole) Thus recordings are not truly linear and the amplitudes of the dA/dt waves are not strictly comparable to each other in the ratios used here and (c) the combination of the balloon elasticity with the magnet inertia has a definite mechanical resonance Because of the above drawbacks data obtained by this method should be considered only as rough approximations of their physiological counterparts and the instrument should not be considered suitable for an accurate estimation of physiological magnitudes

The findings on dC/dt are similar to those on

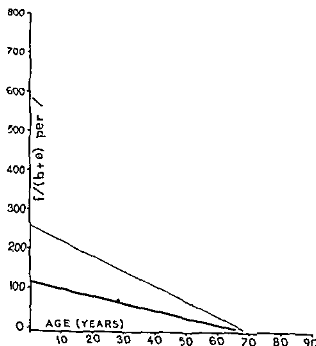


Fig 8 Diagram of f/(b + e) versus age in cases with mitral regurgitation *The thick line* represents average normal and the *thin line* represents the upper normal limits

PEP and EP as measured by standard methods [7] The carotid pulse first derivative has been successfully used for determination of systolic time intervals [13] The baseline is more stable and the inscription of upstroke and nadir points is more sharp in dC/dt than in the carotid tracing The nadir point occurs closer to the aortic second sound in the derivative curve than in the carotid pulse tracing [13] These findings have been confirmed in this Department utilizing the method applied in this work [3]

The systolic intervals measured here were not corrected for pulse transmission time for several reasons (a) the measurement of the intervals was used as an index of the patient diagnosis and not

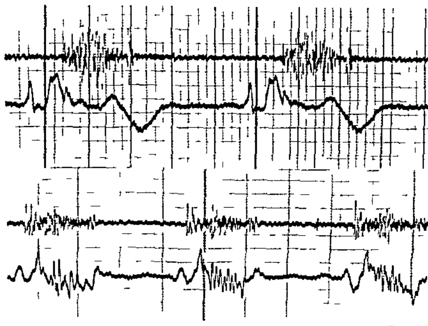


Fig 9 dA/dt (*upper tracing*) and dC/dt (*lower tracing*) in two cases of aortic stenosis with their phonocardiograms Note thrill in dC/dt recording

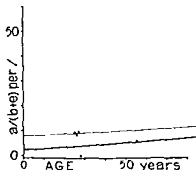


Fig 10 Diagram of a/(b + e) versus age in cases with aortic stenosis *The thick line* represents average normal and the *thin line* represents the upper normal limits

as an accurate estimation of PLP and EP as determined by invasive techniques so that, for the purpose of this work correction was not of primary importance (b) correction for pulse transmission time would involve recordings of three phenomena thus reducing the chief advantage of the method i e its easy bedside applicability (c) the observation error of the difference between two measurements is the sum of the individual errors of these measurements Consequently direct measurement of the Q dC interval has a lower observation error than PFP calculated as the difference between total electromechanical systole minus EP Direct measurement of intervals and sharpness of points measured may compensate for reading errors due to the relatively low paper speed of 50 mm /sec which is commonly available with most portable ECG recorders and (d) at any rate measurement of systolic intervals by classical non invasive methods yields values for PEP and EP that correlate closely with true intervals as recorded by invasive techniques but are not identical to them [11]

The PEP/EP ratio is usually not corrected for heart rate [7] A slight but highly significant effect of R R interval on the (Q dC_1)/(dC_1 dC_2) ratio was noted in the normal group of this study Using a standard method Cokkinos and associates[1] have presented evidence that correction of PEP/EP may be useful

In aortic valve stenosis with or without concomitant AR a (Q dC_1)/(dC_1 dC) ratio lower than normally expected was found similar to the reduction in PEP/EP ratio reported by others [7] The change in this ratio was due to either a shortening in Q dC or a prolongation in dC_1 dC A Q dC_1 interval even shorter than that of AS has been observed only in hyperthyroidism (equal or less than 95 msec in 84 per cent of cases) [11] The contour of dC/dt in aortic valve diseases was pathognomonic

Shortening of dC_1 dC_2 in MR was so marked that finding this interval longer than average should raise some doubt on the diagnosis Shortening of EP in cases with MR has also been

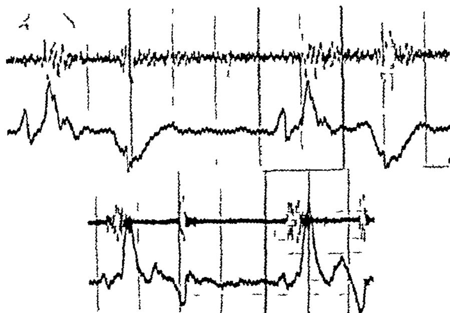


Fig 11 dA/dt and dC/dt in two cases of aortic regurgitation Note double peaked dC/dt tracing

reported by Wanderman and colleagues A shortening of dC dC interval has also been observed in coronary heart disease Contrary to MR ARS was associated with a gross prolongation of the dC dC interval with a fairly high diagnostic efficiency of 0 91

In recent years the apexcardiogram amplitude has been used diagnostically despite an old dispute on its value. Such use has been made by Denef and co workers with the aid of a carefully calibrated instrument or utilizing variously the ratio of the apexcardiogram derivative over the apexcardiogram itself or finally estimating simply the relative amplitude either of the a wave over the total apex cardiogram or of their time derivatives corresponding to an a/b fraction of the terminology used in this paper An expansion of the last method was employed in this work using the ratios of several waves of the dA/dt to each other

The ratios of the diastolic over systolic waves i e the a/(b + e) and f/(b + e) fractions might be considered as semiquantitative expressions of the fourth and third heart sounds respectively To our knowledge the amplitude of a rapid filling wave (f) has not been used diagnostically in a way analogous to that of the atrial (a) wave Comparison with age dependent normal values of these ratios showed results expected from classical knowledge on the fourth and the third heart sounds in valvular diseases Thus a large a/(b + e) ratio dominated in aortic valve lesion especially in AS In most cases this ratio was several times greater than normally expected and a value below the mean normal is seldom seen in AS

An a/(b + e) ratio above normally expected was seen in MR also but the prominent feature in this condition was a high f/(b + e) ratio Again a value of this ratio lower than the age dependent mean normal value should raise suspicion on the diagnosis of pure MR at least of severe degree In MS both diastolic waves were within normal limits

The b/(b + e) fraction could be viewed as an index of the contraction to relaxation speed relationship the exact physiological importance of which is not well known In this work the b/(b + e) fraction was found significantly lower than the rate dependent normal values in aortic valve disease especially in ARS and in MR It has also been found lower than normal in coronary heart disease and in hyperthyroidism No abnormal condition has been observed with a significant increase of the b/(b + e) ratio above that normally expected

The c/(b + e) ratio might prove to be of importance although it reflects a systolic phase of the cardiac cycle that hitherto has not been given proper attention This fraction was increased

above upper normal limits in most cases with MS and was below the mean normal values in all cases with mixed aortic lesion A high c/(b + e) fraction in ARS should reasonably raise the suspicion of concomitant MS It has been suggested that the c wave of dA/dt as recorded by the present method might reflect right ventricular activity[6] The present findings seem to strengthen this view If this hypothesis is true the finding may be of considerable importance since information on right ventricular activity by any non invasive technique is difficult to obtain

It has been shown in this paper that useful parameters may be yielded by an easily applicable bedside non invasive technique These parameters some of which have not been studied by other methods may reflect various aspects of the cardiac function They may be affected by myocardial disease and they may be fairly efficient in differentiating valvular lesions from normal Their usefulness in evaluating myocardial damage in the presence of valvular lesions remains to be seen

Summary

The time derivative of the carotid pulse (dC/dt) and of the apical impulse (dA/dt) was recorded in 137 cases with one valve disease using a simple bedside method The results were compared to those obtained from 103 normal persons The aim of the work was to evaluate quantitatively the deflection changes in valvular heart disease and estimate their diagnostic efficiency A magnet and a coil separated by an air filled balloon were used to obtain dC/dt and dA/dt The potential differences generated in the coil were recorded on a common electrocardiogram (ECG) recorder either photographically at a 75 mm/sec speed together with the phonocardiogram or at a 50 mm/sec paper speed together with the patient s ECG on the same channel The beginning of the QRS (Q) the beginning of the upstroke (dC_1) and the nadir (dC_2) of the dC/dt tracing were easily identified The intervals Q dC_1 and dC_1-dC_2 were found as expected from their analogy to the preejection and ejection intervals respectively The amplitude of the waves a (atrial) b (ventricular contraction) e (ventricular relaxation) f (rapid filling) and c (a negative continuation of the positive b wave) were measured from the isoelectric line on dA/dt In order to evaluate the amplitude of the dA/dt waves they were expressed as fractions of the sum b + e Fraction a/(b + e) was higher than normally expected for the patient s age in mitral regurgitation (MR 23 cases) aortic stenosis (AS 28 cases) aortic regurgitation (AR 22 cases) and double aortic lesion (ARS 14 cases) Fraction b/(b + e) was lower than expected for heart rate in MR AR and ARS Fraction c/(b + e) was higher than expected for heart rate in mitral stenosis (MS 34 cases) and lower than expected in AS and ARS Fraction f/(b + e) was higher than expected for age in MR double mitral lesion (MRS 16 cases) and AR Finally the fraction (a + f)/(b + e) was higher than expected for age in MR MRS AS AR and ARS Parameters with a fair diagnostic efficiency (0 81 to 0 91) were Q dC_1 for AS dC_1 dC_2 for MR and ARS a/(b + e) for AS c/(b + e) for MS f/(b + e) for MR and (a + f)/(b + e) for AR Fraction c/(b + e) was a highly sensitive parameter affected by ARS but with a poor specificity It is concluded that the method may help in the diagnosis of a valvular lesion especially when an easily applicable bedside non invasive technique is needed

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Mitral valve *commissurotomy* versus *replacement*

Considerations based on examination of operatively excised stenotic mitral valves

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Recently we studied 164 operatively excised stenotic mitral valves and by radiography of the excised valve quantitated the amount of calcific deposits in them[1] Of the 164 stenotic valves 14 had absent and 43 had minimal calcific deposits by x ray of the excised valve Of these 57 patients with absent or minimal calcific deposits 37 had moderate to severe mitral regurgitation and therefore clearly deserved mitral valve replacement The remaining 20 had absent or minimal mitral regurgitation absent or minimal calcific deposits and mitral valve replacement nevertheless was carried out This report focuses on these latter 20 patients to ask if mitral valve replacement was preferable to mitral valve commissurotomy

Patients studied

Of the 20 patients 19 underwent mitral valve replacement from 1970 to 1976 and one in 1967 The mitral valve operations on these 20 patients during the 8 years were done by five different surgeons (see Acknowledgment) Certain clinical and morphologic features in the 20 patients are summarized in Table I and morphologic and radiographic features of the excised mitral valves are illustrated in Figs 1 to 5 A radiograph was taken of each of the excised mitral valves via a Field Emission Faxitron x ray unit at 35 KVP No calcific deposits were present in the excised valve in five patients and in the other 15 calcific deposits were trace minimal or mild and in no patient were they visible before operation by routine chest roentgenogram or by fluoroscopy

The 20 patients ranged in age from 36 to 62 years (average 52 years) 12 (60 per cent) were women and eight were men Cardiac catheterization was carried out during the 2 months before mitral valve replacement in all 20 patients (Table I) The mean diastolic pressure gradients between pulmonary artery wedge and left ventricle ranged from 5 to 21 mm Hg (average 11 5 mm Hg) The pulmonary arterial systolic pressures (19 patients) ranged from 32 to 75 mm Hg (average 50 mm Hg) The mean pulmonary arterial wedge pressures ranged from 15 to 35 mm Hg (average 25 mm Hg) In eight patients a systolic pressure gradient was present between left ventricle and systemic artery and it ranged from 10 to 95 mm Hg (average 50 mm Hg) The cardiac index ranged from 1 2 to 3 6 L /min /M² (average 2 09 L /min /M²) Left ventricular angiography in 19 patients indicated minimal (1+/4+) mitral regurgitation in 16 patients and no regurgitation in three patients The one patient (No 10 Table I) in whom left ventricular angiography was not performed had no precordial systolic murmur Injection of contrast material into the aortic root in 18 patients indicated various degrees of aortic regurgitation in 14

In addition to mitral valve replacement the aortic valve was replaced in 12 (60 per cent) of the 20 patients and the tricuspid valve in four (20 per cent) three of whom also had aortic valve replacement The average mean diastolic pressure gradient between pulmonary arterial wedge post

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Table I Clinical and hemodynamic data in the 20 patients analyzed

	Surgical Number	Age (yrs)	Sex	Interval MVC to MVR (yrs)	PAW LV mdg (mm Hg)	PA (s/d) (mm Hg)	CI (L/min /M)	MR by LV cine (0-4+)	MV Ca by x ray of excised valve (0+ 4+)	LV SA PSG (mm Hg)	AR by AA cine (0-4+)	AVR	TVR	Fig No
No previous mitral valve commissurotomy														
1	67-3005	36	M	–	8	32/10	1 7	1+	1+	26	2+	+	0	–
2	70-3094	47	M	–	11	50/20	1 8	1+	1+	0	2+	+	0	–
3	70-3127	44	F	–	15	45/32	1 7	1+	1+	10	3+	+	+	–
4	72-4096	57	F	–	5	34/18	2 0	0	0	40	4+	+	0	–
5	73-5085	60	M	–	17	–	1 5	1+	1+	0	3+	+	0	–
6	74 5139	48	M	–	12	50/20	3 1	0	1+	50	3+	+	0	–
7	75-5067	52	F	–	21	60/30	2 3	1+	0	90	2+	+	+	–
8	75-5106	58	M	–	10	70 40	3 6	1+	0	0	0	0	0	1
9	76-28	58	M		12	40/20	2.3	1+	1+	0	0	0	0	–
Previous mitral valve commissurotomy														
10	71 3125	59	F	17 & 14	11	36/18	1 7	–	1+	0	–	0	0	2
11	71-3136	62	F	15	11	48/23	2 6	1+	1+	0	1+	0	0	3
12	71 3144	61	F	19	10	70/35	3 4	1+	1+	0	1+	0	0	4
13	72 5003	64	F	10	15	5/35	1.2	0	1+	0	1+	0	0	–
14	73 5032	57	F	12	8	55/25	2.3	1+	1+	0	0	0	0	–
15	73 5071	49	M	18	10	50/20	2 2	1+	1+	95	2+	+	0	–
16	74-5047	47	M	2	14	45/24	2 5	1+	1+	0	2+	+	0	–
17	74-5156	36	F	8	7	40/20	1 0	1+	0	75	–	+	+	5
18	75-5162	43	F	15 & 8	10	55/25	1 7	1+	1+	0	0	0	+	
19	76 95	51	F	6	16	55/28	2 0	1+	1+	10	2+	+	0	–
20	76 99	42	F	4	7	32/15	1 2	1+	0	0	3+	+	0	–

At cardiac catheterization performed during the 2 months before mitral valve replacement

Left atrial press re

A precordial systolic murmur w absent

Abbreviat ns AA = *asce ding aorta* AR = *aortic regurgitation* AVR = aortic alve replacement CI = cardiac index F = f male LA = left atrial LV = left entricular M = male mdg = mean diastolic gradient MR = mitral regurgitation MV = mitral valve MVC = mitral val e commissur tomy MVR = mitr l val replacement PA = pulmonary arterial PAW = pulmon ry arterial wedge PSG = peak systolic gradient SA = systemic arterial s/d = systolic/diastolic TVR = tricuspid valve replacement

tion and left ventricle in the patients who underwent aortic valve replacement was 11 9 mm Hg and in those in whom this valve was not replaced it was 10 9 mm Hg

Of the 20 patients 11 had had mitral commissurotomy from 2 to 19 years (average 12 years) previously Two patients (No 10 and No 18 Table I) had had two previous commissurotomies The pulmonary arterial wedge to left ventricular mean diastolic pressure gradients in these 11 patients ranged from 7 to 16 mm Hg (average 10 8 mm Hg) whereas this gradient in the nine patients without previous commissurotomy ranged from 5 to 21 mm Hg (average 12 3 mm Hg)

Thrombus was found in the body of left atrium at the time of valve replacement in two patients (No 10 and No 18 Table I)

Comments

The absence of significant calcific deposits (as determined by radiography of the excised valve) and the absence of significant mitral regurgitation (as determined by left ventricular angiography) in the operatively excised stenotic mitral valves described above raises the question as to whether mitral valve replacement in these 20 patients was preferable to commissurotomy To answer this question the stenotic mitral valves in patients having only commissurotomy would have to be studied morphologically and radiographically in the same manner as the valves which were excised and replaced Obviously the non-excised valve cannot be examined in the same manner as the excised valve Nevertheless the ideal valve for mitral commissurotomy in the past has been considered to be the stenotic one

Fig. 1. a through d. Case No. 8 (Table I). a, Radiograph showing no calcific deposits. b, View of anterior leaflet and papillary muscles from left ventricle. The papillary muscles are covered by thick fibrous tissue. c, View from left atrium. d, View of orifice from left ventricle again showing the thick fibrous tissue overlying the papillary muscles.

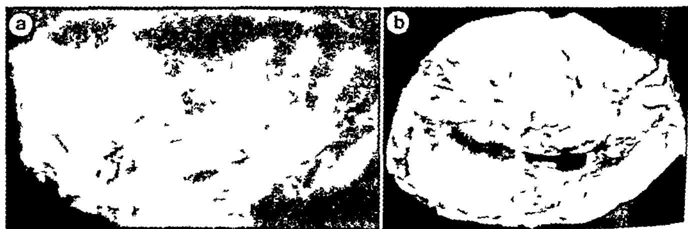


Fig. 2. a and b. Case No. 10 (Table I). a, Radiograph showing two calcific deposits. b, View from left atrium.

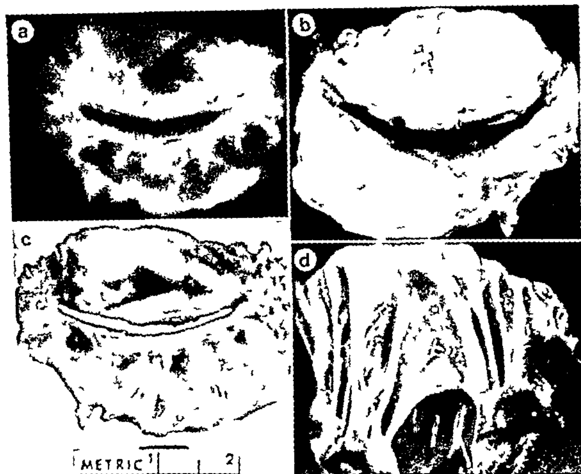


Fig 3 a through d Case No 11 (Table I) a Radiograph showing three minute calcific deposits. b View from left atrium c View from left ventricle after excision of the chordae tendineae d View of anterior leaflet from left ventricle

which is free of calcific deposits free of significant mitral regurgitation and mobile[2] The excised mitral valves in the 20 patients analyzed here were free of calcific deposits by preoperative examination and none had significant mitral regurgitation by preoperative evaluation Mobility of the mitral valve at the time of valve replacement was described in the operative note in six of the 20 patients and in each mobility was limited particularly so in four patients Small calcific deposits in the mitral leaflets however were noted at operation in 10 patients in three others calcific deposits were noted to be absent and in the remaining seven patients no mention was made in the operative note regarding their presence or absence Radiography however of the excised valve disclosed no calcific deposits in five patients and minimal deposits in 15 In two of the patients stated to have calcific deposits in the mitral valve at operation radiography of the excised valve disclosed no calcific deposits indicating that palpation and visual inspection is not always accurate with respect to calcific deposits

It seems likely that all 20 patients analyzed here would have been acceptable candidates for mitral commissurotomy alone in the pre valve replacement era Why then was mitral valve replacement rather than commissurotomy carried out? One factor certainly was the fact *that one or more other valves were replaced* Thirteen of the 20 patients also underwent replacement of the aortic or tricuspid valve or both Under these circumstances mitral replacement may be advisable rather than risk possible significant regurgitation or incomplete relief of the stenosis by mitral commissurotomy

Another consideration was the fact that *cardiopulmonary bypass was utilized* in each patient This procedure obviously allows visual

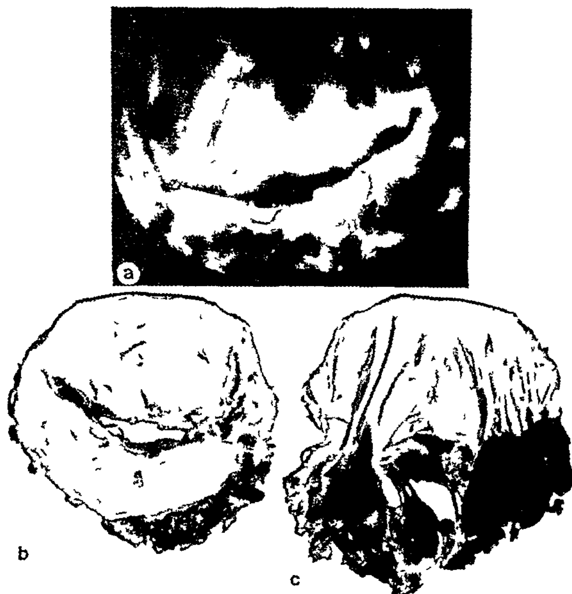


Fig 4 a through c Case No 12 (Table I) *a* Radiograph. *b* View from left atrium *c* View of anterior leaflet and papillary muscles from left ventricle

inspection of the valve something not possible when commissurotomy was done as a "closed" procedure We suspect that the visually inspected stenotic mitral valve is more frightening to the observer than is the stenotic valve which is only palpated Thus visual inspection alone particularly when valve replacement is a reasonable and uncriticized option may push the surgeon in some patients toward replacement rather than simple commissurotomy

Another factor was *relatively little experience of some surgeons with mitral commissurotomy* particularly as an open procedure compared to valve replacement Of the 20 study patients 17 were operated upon by surgeons less than 40 years of age when the operation was done The younger surgeons have had less experience with the commissurotomy procedure than with valve replacement and consequently may feel more comfortable with the latter procedure

Another factor was *displeasure with the attempted commissurotomy* Three patients (No 3 No 4 and No 6 Table I) had open mitral commissurotomy attempted but the surgeon was not satisfied with his results and valve replacement therefore was done

And finally *previous mitral valve commissurotomy* probably contributed to the decision Eleven of the 20 patients had had at least one previous mitral commissurotomy Examination of the

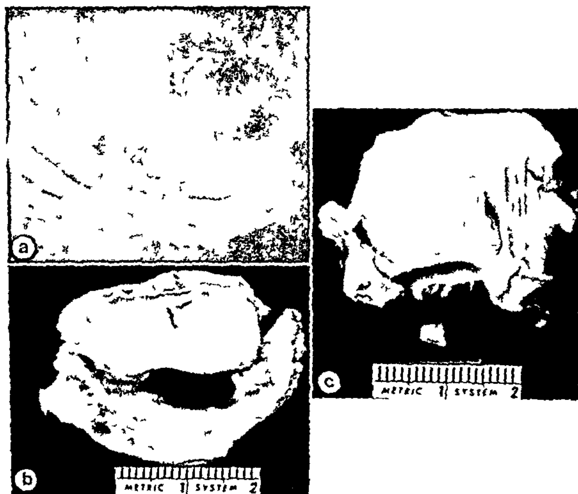


Fig 5 a through c Case No 17 (Table I) a Radiograph showing no calcific deposits b View from left atrium c View of anterior leaflet from left ventricle

excised mitral valve in several of these 11 patients however, showed no anatomic residua of the previous commissurotomy Therefore as is already recognized a mitral valve which has had one previous commissurotomy and later becomes severely stenotic again can nevertheless have another commissurotomy so long as calcific deposits are absent and mitral regurgitation is absent or is minimal

Thus as emphasized recently by Spencer[17] the relative frequency of mitral valve reconstruction (i e commissurotomy) versus replacement will vary not only with the experience and attitude of the surgeon but with the type of valve pathology seen a surgeon experienced and enthusiastic about reconstruction might perform commissurotomy in 95 per cent of cases if patients are referred for operation with relatively early disease while a similar surgeon might find it necessary to perform replacement in over 30 per cent of cases if patients are referred only with far advanced disease and extensive calcification [17] Nevertheless the definition of advanced disease appears to be changing but as yet there is insufficient information to know whether this apparent change will prove to be beneficial or detrimental to the patient

Summary

Among 164 patients who underwent mitral valve replacement because of mitral stenosis (with or without mitral regurgitation) and had radiographs taken of their operatively excised mitral valves 20 had absent or minimal calcific deposits in the excised valves and absent or minimal mitral regurgitation as determined except for one patient by left ventricular angiography preoperatively This report focuses on

these 20 patients to ask if mitral valve replacement was preferable to mitral valve commissurotomy Although in the pre valve replacement era, all 20 patients almost surely would have been considered good candidates for mitral commissurotomy, other factors namely the need to replace one or more other cardiac valves (13 patients) the utilization of cardiopulmonary bypass allowing visual inspection rather than simple palpation of the diseased mitral valve (all 20 patients) relatively little experience with mitral commissurotomy in four of the five surgeons (17 patients), displeasure with attempted commissurotomy (three patients) previous mitral commissurotomy (11 patients) and incorrect identification of mitral calcific deposits (two patients) each contributed in one or more patients to the final decision of replacement versus commissurotomy Even though mitral commissurotomy has been in use for 30 years, the mere alternative of valve replacement may have altered somewhat the definition of the stenotic mitral valve previously considered ideal for mitral commissurotomy

The authors are indebted to the five surgeons who operated on the 20 patients analyzed in this report These surgeons and the number of patients operated on by them were the following Charles L McIntosh (7) Lawrence L Michaelis (7) Andrew G Morrow (3) Robert L Reis (2) and Edward B Stinson (1) We thank Dr Andrew G Morrow for reviewing the manuscript and Dr Stephen E Epstein for free use of the hemodynamic data in the study patients

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Pre- and postoperative hemodynamic and cineangiocardiographic assessment of left ventricular function in patients with aortic regurgitation

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Valvular surgery has evolved considerably during the past decade making operations safer and valve dysfunction less frequent However such operations are still marred by a certain number of early deaths incomplete results and late post operative deaths Several investigators have attempted to define the long term prognostic significance of various preoperative parameters Among the factors responsible for operative failures myocardial status appears to be determinant In aortic regurgitation (AR) the mechanical overloading caused by the regurgitation induces myocardial insufficiency which is often severe as demonstrated by the decrease in left ventricular function (LVF) indices measured by angiocardiography as well as by echocardiography These myocardial alterations have recently been confirmed by ultrastructural studies

The long term postoperative course of these indices of LVF in AR has been the object of only a limited number of studies Gault and associates and Henry and colleagues consider myocardial alterations to be irreversible

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In this study hemodynamic and angiocardiographic parameters were assessed before and after valve replacement in order to provide evidence that at least in some cases myocardial insufficiency is reversible

Materials and methods

A hemodynamic and angiocardiographic study was performed in 11 patients with AR prior to and 14 months on the average (range 7 to 25 months) following aortic valve replacement There were 10 male patients and 1 female patient whose ages ranged from 21 to 62 years (mean 39 ± 14 years) The etiology was rheumatic in six patients rheumatoid spondylitis in one bacterial endocarditis in one calcified bicuspid valve in one Marfanoid valve in one and unknown in one

In nine cases surgery was justified because of more or less severe symptoms of left ventricular failure with angina pectoris in two cases Two asymptomatic patients were referred for surgery owing to markedly altered LVF with striking cardiac enlargement (CTR ≥ 0 64) Cardiothoracic ratio was increased (≥0 50) in all patients but two In all cases valve correction was complete and the integrity of the mitral valve was confirmed

Preoperatively all patients underwent left and right cardiac catheterization after mild premedi

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Table 1 Pre and postoperative results

Patients	Age (yrs)	Time surgery → catheter (months)		CTR (%)	RR (ms)	CI (L/min./M²)	AoSP (mm Hg)	AoDP (mm Hg)	EDP* (mm Hg)	RF (%)	LVSW (gr M/ beat)
1	38	Preop	1.5	0.55	1250	2.5	125	35	16	5?	1[illegible]
		Postop	25	0.45	840	4.2	130	66	9	—	11
2	62	Preop	0.5	0.62	720	3	140	40	—	73	2[illegible]
		Postop	19	0.53	720	2.65	145	68	6	—	5[illegible]
3*	27	Preop	3	0.44	680	3.2	135	50	18	74	[illegible]
		Postop	15	0.38	620	3.7	105	75	6	—	[illegible]
4	33	Preop	1	0.69	710	2.4	120	60	28	75	1[illegible]
		Postop	15	0.61	600	2.85	105	80	12	—	1[illegible]
5	41	Preop	1.5	0.55	720	2.2	160	50	20	78	1[illegible]
		Postop	14	0.4	650	3	115	75	5	—	33
6	49	Preop	1	0.50	730	3	145	60	25	60	149
		Postop	8	0.44	620	3.2	150	100	8	—	103
7‡	56	Preop	5	0.52	850	1.9	160	60	20	72	17[illegible]
		Postop	7	0.50	620	4.3	140	90	10	—	101
8	26	Preop	1	0.60	750	1.6	120	40	25	68	10[illegible]
		Postop	13	0.65	740	1.8	125	85	33	—	—
9*	21	Preop	0.5	0.65	650	3.65	130	50	27	65	1[illegible]
		Postop	17	0.5[illegible]	910	3.05	120	60	9	—	94
10*‡	23	Preop	1.5	0.48	500	—	9	50	14	—	[illegible]
		Postop	10	0.49	620	2.3	65	66	10	—	69
11*	54	Preop	3	0.64	1000	2.4	140	60	10	51	1[illegible]9
		Postop	8	0.60	780	2.3	110	70	10	—	70
m	39	Preop	1.6	0.57	754	2.6	132	50	20	67	1[illegible]
sd	14		1.4	0.09	210	0.6	19	9	5	10	[illegible]
m		Postop	14	0.51	698	3.1	121	81	11	—	66
sd			5.4	0.09	110	0.8	20	10	6	—	25
m	27	Controls	—	0.49	744	3.2	114	78	8.6	—	72
sd	13			0.05	145	0.6	10	11	2.4	—	20
P (Pre vs. postop)			—	NS	NS	NS	NS	0.001	0.05	—	0.01
P (Pre vs. controls)			—	0.001	NS	0.05	0.05	0.001	0.01	—	0.01
P (Post vs. controls)			—	0.001	NS	NS	NS	NS	NS	—	NS

EDP was assimilated to P_{cp} postoperatively

* = asymptomatic patients

= cardiothoracic ratio < 0.55

‡ = perioperative infarction

Abbreviations CTR = cardiothoracic ratio RR = cardiac cycle CI = cardiac index AoSP = aortic systolic pressure AoDP = aortic diastolic pressure EDP = left ventricular end-diastolic pressure RF = regurgitant fraction LVSW = total left ventricular stroke work, LVSW = net left ventricular stroke work, LV mass = left ventricular mass EDV = left ventricular end-diastolic volume ESV = left ventricular end-systolic volume EF = ejection fraction ΔD = extent of shortening LVET = left ventricular ejection time VCF = mean velocity of fiber shortening MLVEP = mean left ventricular ejection rate L/D = diastolic axis ratio L/D = systolic axis ratio P_{cp} = mean pulmonary capillary pressure m = mean sd = standard deviation preop = preoperative post = postoperative

cation with 5 to 10 mg. of diazepam. None of these patients had received cardiac tonic or diuretic drugs for at least 48 hours

Pressures were recorded with a Statham P 23 DB transducer In one patient the left ventricle (LV) could not be catheterized In all cases but one cardiac output was measured using Fick's method All patients also underwent right anterior oblique (RAO) single plane cineaortography (100 frames per second) The contrast medium (Radioselectan 76 per cent) was injected in a dose of 1.5 cm³/kg. over 3 to 4 seconds and an electrocardiogram and aortic pressure were recorded simultaneously Coronary arteriography was performed in only one patient 41 years of age the others being less than 40 years old

The cineangiograms were displayed using a Tage Arno 35 mm projector Either the third or fourth cycle was studied so as to avoid the Starling effect initially and later myocardial toxicity and hypervolemia due to the contrast medium Extrasystolic and post-extrasystolic cycles were excluded. All patients exhibited sinus rhythm Left ventricular surface area was

LVSW (g.m/M² / beat)	LV (g/M²)	EDV (cm³/M²)	ESV (cm³/M²)	EF (%)	ΔD (%)	LVET (ms)	VCF (circ/s)	MLVER	L/D	L/D
126	290	224	110	49	22	300	0.60	1.36	1.56	1.67
108	211	107	71	66	36	260	1.27	2.54	1.98	2.53
—	—	216	134	62	34	320	1.07	1.94	1.48	2.02
57	—	58	33	56	25	320	0.87	1.75	1.70	2.02
175	—	209	140	67	36	350	1.02	1.91	1.47	1.85
87	—	70	52	74	45	260	1.74	2.85	1.86	2.99
114	350	392	116	30	14	370	0.39	0.81	1.3	1.55
111	202	255	78	30	15	290	0.55	1.07	1.19	1.27
166	185	208	121	58	24	320	0.76	1.81	1.65	1.90
32	64	39	23	60	32	270	1.17	2.22	1.41	1.57
111	—	174	91	51	24	320	0.77	1.59	1.47	1.67
98	—	84	49	58	31	240	1.31	2.42	1.67	2.22
151	203	228	101	44	20	330	0.62	1.33	1.55	1.73
93	132	91	52	57	30	220	1.40	2.59	1.72	2.25
78	—	468	63	13	30	330	0.10	0.39	1.26	1.21
—	—	—	—	—	—	305	—	—	—	—
123	—	350	117	33	15	320	0.43	1.03	1.50	1.64
91	—	122	79	65	37	320	1.16	2.03	1.94	2.60
62	124	202	65	32	15	290	0.53	1.14	1.77	1.94
62	174	247	52	21	9	270	0.33	0.78	1.51	1.57
148	—	221	82	37	15	300	0.52	1.23	1.26	1.22
62	—	234	54	23	11	270	0.41	0.85	1.35	1.47
135	231	242	108	45	21	320	0.66	1.32	1.51	1.65
39	89	70	23	13	8	20	0.20	0.45	0.14	0.24
80	157	131	54	51	47	270	1.03	1.91	1.63	2.11
25	60	83	18	19	12	30	0.47	0.76	0.25	0.56
66	74	81	52	65	35	275	1.29	2.37	1.65	2.14
20	8.8	12	8	6	5.2	25	0.28	0.39	0.23	0.32
0.01	NS	0.01	0.001	NS	NS	0.01	0.02	0.05	NS	0.05
0.001	0.01	0.001	0.001	0.001	0.001	0.01	0.001	0.001	0.05	0.001
NS	0.02	NS	NS	0.05	0.05	NS	NS	NS	NS	NS

measured by planimetry and LV volumes were calculated by the area-length method of Dodge and Sandler after adjustment for radiologic enlargement and distortion the coefficient being determined by means of a grid positioned at the mid thoracic thickness

The following parameters were determined on the basis of angiographic data extent of shortening of the small axis (ΔD) expressed as a percentage of end-diastolic length left ventricular end diastolic and end systolic volumes (EDV and ESV) expressed in cm³/M² from which the stroke volume (cm³/M²) was determined SV = ESV − EDV ejection fraction (EF) expressed as a percentage EF = SV/EDV mean left ventricular ejection rate (MLVER) or the quotient of EF and left ventricular ejection time (LVET) (MLVER = EF/LVET) regurgitant fraction (RF) determined from the SV values obtained by angiography and by Fick's method (SV ,) expressed as a percentage RF = (SV − SV ,)/SV mean velocity of circumferential fiber shortening ($\overline{VCF}$) expressed in circumferences per second $\overline{VCF}$ = ΔD/LVET end diastolic and end systolic axis ratios (L/D, and L/D) left ventricular stroke work (LVSW) expressed in g.m/M²/beat determined from mean left ventricular or aortic systolic pressure ($\overline{LVSP}$ or AoSP) obtained by planimetry and angiographic SV LVSW = $\overline{LVSP}$ × SV × 0.0136 net left ventricular stroke work obtained by subtracting EDP from $\overline{LVSP}$ LVSW = ($\overline{LVSP}$ − EDP) × SV × 0.0136 In five patients left ventricular mass was evaluated from EDV and anterior wall thickness the epicardial contour being delineated by the anterior interventricular artery

Postoperatively right cardiac catheterization

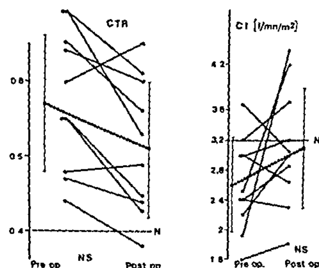


Fig 1 Pre and postoperative values of cardiothoracic ratio (*CTR*) and cardiac index (*CI*) The P values refer to the difference between pre and postoperative measurements *N* = mean normal value *Open circles* = mean pre and post operative values ± one standard deviation

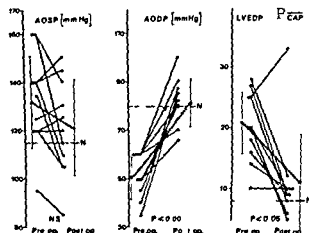


Fig 2 Pre and postoperative values of aortic peak systolic pressure (*AoSP*) aortic diastolic pressure (*AoDP*) and left ventricular filling pressure left ventricular end-diastolic pressure (*LVEDP*) before surgery and mean pulmonary capillary pressure ($\overline{P}$) after surgery (see *Fig 1* for explanation of symbols)

and recording of aortic pressure were performed in all patients combined with pulmonary arteriography in ten patients and aortography in five clinical examination having definitely ruled out any suspicion of residual AR in the other six patients LVF was evaluated from the levogram phase of pulmonary arteriography the cycle chosen being the earliest possible before the fifteenth second so as to overcome the secondary effects of the contrast medium The parameters studied were the same as before surgery In one

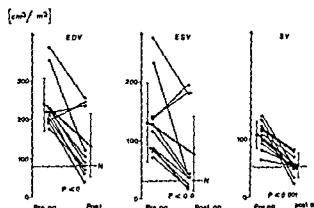


Fig 3 Pre and postoperative values of left ventricular end diastolic volume (*EDV*) end systolic volume (*ESV*) and stroke volume (*SV*) (see *Fig 1* for explanation of symbols)

patient with severe heart failure angiograph was not performed

The indications for postoperative control investigations were not selective in this series patient acceptance and a follow up of more than months being the criteria used Comparison between pre and postoperative values was performed by means of Student s t test for paired series and these values were also compared to those of 20 controls with no evidence of left ventricular abnormalities Calculations were done on a Hewlett Packard HP 65 calculator

Results

Pre and postoperative results are shown in Table I and in Figs 1 to 5 Comparison of pre and postoperative values for the various parameters is mentioned in each figure

Hemodynamic parameters All patients improved following surgery and all but one became asymptomatic Cardiac index (CI) significantly reduced prior to surgery (2 6 ± 0 6 L/min/M $p < 0.05$) returned to normal (3 1 ± 0 8 L/min/M) Three patients however retained a markedly reduced cardiac output (CI ≤ 2 3 L/min/M) Pulmonary artery systolic pressure was normal prior to surgery and did not change postoperatively (24 ± 6 vs 24 ± 14 mm Hg) The same was true of mean pulmonary capillary pressure ($\overline{P}$) (11 ± 4 vs 11 ± 8 mm Hg) AoSP slightly increased prior to surgery (132 ± 1[illegible] $p < 0.05$) returned to normal (121 ± 20 mm Hg) while mean aortic systolic pressure remained constant (117 ± 21 vs 122 ± 20 mm Hg) as did systemic vascular resistance (1 68[illegible] ± 646 vs 1 5[illegible]7 ± 388 dynes s cm)

Aortic diastolic pressure (AoDP) severely reduced prior to surgery ($p < 0.01$) reverted to normal (50 ± 9 vs 81 ± 10 mm Hg). EDP increased before valve replacement ($p < 0.01$) with an inverted LV to capillary gradient in eight cases reverted to normal (20 ± 5 vs 11 ± 8 mm Hg). Following surgery $\overline{P}_{p}$ was assimilated to EDP.

LVET significantly increased before surgery (320 ± 20 msec, $p < 0.01$) reverted to normal after surgery (270 ± 30 msec). The same was true of $LVSW_T$ which dropped from 165 ± 52 ($p < 0.01$) to 86 ± 28 g m/M /beat and LVSW which decreased from 135 ± 39 ($p < 0.001$) preoperatively to 80 ± 25 g m/M /beat postoperatively.

Angiographic data. Left ventricular volumes were markedly increased prior to surgery ($p < 0.001$): EDV = 242 ± 70 cm /M and ESV = 135 ± 68 cm /M. These volumes declined significantly but did not return to normal levels following valve replacement: EDV = 131 ± 83 cm /M² (NS) and ESV = 76 ± 75 cm /M ($p < 0.01$). In three patients ventricular volumes did not decrease. SV also significantly increased before surgery, 108 ± 23 cm /M ($p < 0.001$) returned to normal 54 ± 18 cm /M. The preoperatively augmented left ventricular myocardial mass (LV_m) (231 ± 89 g/M, $p < 0.01$) declined after surgery but remained above the normal level (157 ± 60 g/M, $p < 0.02$).

Determination of L/D_i and L/D revealed that the abnormally spherical left ventricle ($L/D_D = 1.51 \pm 0.14$, $p < 0.05$; $L/D_s = 1.70 \pm 0.20$, $p < 0.001$) assumed its normal shape after surgery ($L/D_i = 1.63 \pm 0.26$ and $L/D = 2.11 \pm 0.56$).

LVF indices which were all significantly ($p < 0.001$) depressed prior to surgery ($\Delta D = 21 \pm 8$ per cent, EF = 46 ± 13 per cent, $\overline{VCF} = 0.68 \pm 0.2$ circ/sec, MLVER = 1.32 ± 0.48) increased following surgery. However ΔD and EF remained significantly ($p < 0.05$) low ($\Delta D = 27 \pm 12$ per cent and EF = 51 ± 19 per cent) whereas normalized LVF indices returned to virtually normal levels: $\overline{VCF} = 1.03 \pm 0.47$ circ/sec and MLVER = 1.91 ± 0.76.

Examination of individual values for these parameters revealed that preoperative LVF indices were normal in only two patients, moderately decreased in two others, and markedly depressed in the seven remaining patients ($\Delta D < 24$ per cent, EF < 50 per cent, $\overline{VCF} < 0.75$ circ/sec and MLVER < 1.6). Following surgery these indices remained abnormally low in four patients. In three patients persistently depressed values were definitely established (two of these patients sustained an acute myocardial infarction during the immediate postoperative period) and in one case they were highly probable in view of the marked elevation of $\overline{P}_{p}$ though angiography was not performed in this patient.

Among the three patients without significant preoperative myocardial abnormalities the contractile status of the myocardium was normal

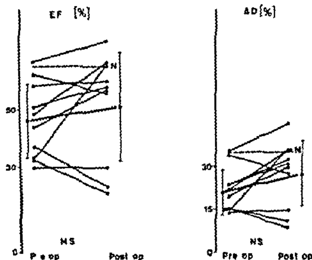


Fig 4 Pre and postoperative values of ejection fraction (*EF*) and extent of circumferential fiber shortening (*ΔD*) (see *Fig 1* for explanation of symbols)

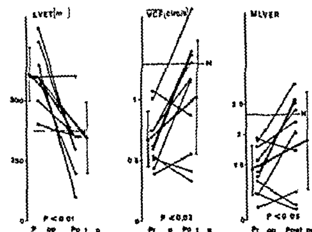


Fig 5 Pre and postoperative values of left ventricular ejection time (*LVET*), mean velocity of circumferential fiber shortening ($\overline{VCF}$) and mean left ventricular ejection rate (*MLVER*) (see *Fig 1* for explanation of symbols)

after valve replacement with slight depression of LVF indices in one patient

Thus in four patients with severely depressed LVF prior to surgery dramatic improvement was documented following correction of the valvular defect

Discussion

This study was confined to patients with isolated pure chronic aortic regurgitation without evidence of associated aortic stenosis (systolic left ventricular-aortic gradient always less than 10 mm Hg) Limiting the study to this category of patient made it possible to assess more accurately the nature of left ventricular disturbances and their postoperative course since left ventricular myocardial adaptation mechanisms in aortic regurgitation and stenosis differ considerably Only patients with complete correction of the valvular defect were included in this study to exclude the possibility of residual mechanical overloading

Preoperative evaluation of all patients included catheterization of both the left and right sides of the heart but after surgery it was deemed inopportune to perform transseptal catheterization in asymptomatic patients After complete correction of regurgitation in patients without any mitral valve disease confirmed by surgery the left ventricular filling pressure can be assimilated to $\overline{P}$ and the validity of quantitative left ventricular angiography using the levogram phase of pulmonary arteriography has been proved

Hemodynamic changes The spectacular symptomatic improvement often seen following complete valve repair in the absence of valve dysfunction is related to improved hemodynamic status This was reflected in an increase of AoDP a return to normal of EDP and CI and a decrease in LVSW without significant change in AoSP

However in our patients CI remained low in three patients One of these patients exhibited only transient symptomatic improvement and had persistent marked cardiomegaly (CTR = 0 65) accentuation of electric LV hypertrophy and elevated $\overline{P}$ All these signs are suggestive of severe irreversible myocardial insufficiency

Changes in left ventricular volumes and mass Considerable LV dilatation is a common finding in severe chronic AR as evidenced by the various series reported in the literature[11] In our series the mean EDV was approximately threefold the normal value exceeding 200 cm³/M in all but one patient Three factors are involved in this dilatation the regurgitant volume the duration of aortic regurgitation and myocardial status Kennedy and colleagues[1] observed a close correlation (r = 0 91) between EDV and RF at least in the absence of myocardial insufficiency If myocardial alterations supervene however EDV becomes excessively increased and the LV becomes abnormally spherical especially during end systole as evidenced by the highly significant decrease in L/D ($p < 0.001$) prior to surgery

In our series which included only patients with severe regurgitation (RF = 67 ± 10 per cent) and severe myocardial impairment in most cases there was no correlation between these two parameters The influence of the duration of regurgitation on LV dilatation appears to be very difficult to evaluate owing to the inaccuracy in establishing the exact time of onset of the disturbance since in chronic AR patients become symptomatic rather late There is a general consensus among investigators as to the absence of correlation between EDV and EDP Indeed it has been proved that in chronic dilatation both experimental and clinical LV rigidity decreases

Complete surgical repair results in a spectacular decrease of LV volumes assessed simply by measuring CTR although in our series unlike others there was no correlation between these two parameters When regurgitation is suppressed SV returns to normal while EDV and ESV remain moderately increased

Reduced volume is paralleled by a tendency of the LV to reassume its normal geometry The circumferential muscle fibers once again become preponderant over the longitudinal fibers during contraction Whereas the mean LV volumes decreased markedly in our series it is noteworthy that four patients had persistently increased EDV and ESV despite reversion of SV to normal In one of these patients EDV and ESV diminished but only moderately in two patients there was an increase (these two patients sustained an acute myocardial infarction during the immediate postoperative period) and the last patient did not undergo angiocardiography but had cardiac enlargement following surgery

Left ventricular mass LV dilatation in AR is attended by a marked increase in LV_m the *hypertrophy-dilatation* being considerable in some cases Unlike aortic stenosis in which diminution of myocardial mass following valve replacement has been conclusively demonstrated it is not clear whether this is the case for AR

In our series we observed a significant decrease in the mean values but wall thickness was measured in only five cases Although the use of the RAO view has been criticized for measuring wall thickness we nevertheless feel that it is a valid technique insofar as the patient serves as his own control

Changes in left ventricular function Marked LV dilatation is paralleled by profound alterations of LVF as emphasized by several investigators In our series before surgery LVF indices were normal in two patients and altered in nine five of whom had very severely impaired LVF There was a fairly close correlation (r = 0 60) between EDV and LVF indices The greater the dilatation of the LV the more severe the decrease in LVF indices

When LV dilatation is moderate and LVF indices are normal or close to normal at rest a number of tests may be used to demonstrate impaired performance

Very few studies have been devoted to the long term postoperative follow up of LVF indices Gault and associates studied the velocity of fiber shortening at peak stress prior to and following valve replacement in five patients with AR and found no changes Henry and colleagues came to the same conclusion using echocardiography In contrast Kennedy and co workers noted improvement in some cases In our series mean values of EF and ΔD increased moderately while mean values of $\overline{VCF}$ and MLVER rose markedly

Examination of individual values revealed that LVF indices remained very low in four patients despite lasting symptomatic improvement in three cases and transient improvement in one case In two of these patients (28 and 54 years old) with no clinical evidence of coronary artery disease persistent impairment of LVF may be accounted for by the onset of myocardial infarction immediately following valve replacement In the other two patients failure to improve might have been due to irreversible myocardial damage caused by the mechanical overloading

In six patients however LVF indices were normal after surgery Only one of these patients had normal LVF prior to surgery In five patients therefore LV performance improved following valve replacement and it is noteworthy that one of these had extremely severe LVF impairment before surgery

These changes prove that LV performance may improve after successful aortic valve surgery even when myocardial insufficiency is severe

In one patient who had normal LVF before valve replacement there was a moderate decrease in LVF indices which remained however within normal limits No postoperative complications occurred in this patient As for the two asymptomatic patients referred for surgery because of marked cardiomegaly and severely impaired LVF one had a return to normal LVF whereas the other showed no improvement but this latter patient sustained a myocardial infarction after surgery

Changes in myocardial function Does the possibility of improved LVF subsequent to suppression of mechanical overloading reflect reversal of myocardial alterations which are virtually constant in severe chronic AR?

Evaluation of myocardial function is based on two classes of indices pressure and fiber shortening Indices involving pressure appear to be open to criticism in AR owing to the shortness of the isovolumic contraction phase Our study is based on indices involving fiber shortening during the ejection phase Theoretically the velocity of fiber shortening at peak stress is the most accurate index but in practice it is extremely complex to assess and has therefore been replaced by the simpler $\overline{VCF}$ with which it has been shown to correlate closely However in AR this index appears to us to depend not only on the myocardial contractile state but also on extramyocardial factors It does indeed depend on ΔD and on the duration of LV ejection which is markedly increased in this disorder Hence depression of myocardial function as assessed by $\overline{VCF}$ prior to surgery may be enhanced by lengthening of LV ejection Following valve repair however $\overline{VCF}$ no longer suffers from this drawback

To evaluate the changes in myocardial function it is therefore necessary to study the relative variations of both LVF indices and extramyocardial factors

Before surgery mean values of $\overline{LVF}$ indices

were significantly reduced despite two facilitating factors (1) increased end diastolic fiber lengthening the fibers working at their optimal length that is at the peak of Starling s force-length relationship is one considers the experimental investigations on chronic LV dilatation and (2) a probable decrease in impedance to ventricular ejection at least during early systole (decreased AoDP) with a slight increase in AoSP, systemic vascular resistance being normal These findings demonstrate that myocardial alterations are usually profound in severe chronic AR

After surgery mean values of LVF indices increased despite two adverse factors heart rate remaining unchanged (1) reduced end diastolic fiber stretching though changes in preload do not appreciably influence VCF, and (2) increased impedance to ejection with return to normal of AoDP and nearly no change either in AoSP or in systemic vascular resistance

In view of the relative variations of LVF indices and extramyocardial factors influencing LV mechanics it may be concluded that there is postoperative improvement of actual myocardial function in some cases All patients whose EF was diminished but exceeded 40 per cent had normal LVF following surgery whereas in the other cases no improvement was detected

Irreversible myocardial insufficiency in the absence of preoperative coronary heart disease may therefore be the result of two major factors (1) myocardial damage caused by intraoperative or immediate postoperative complications inadequate myocardial protection or coronary embolism and (2) severe irreversible myocardial damage prior to surgery related to LV mechanical overloading The severity of such lesions has been proven by ultrastructural studies

It is not possible at present to define a threshold below which preoperative lesions are irreversible even when LVF indices are extremely poor *(EF = 30 per cent) prior to surgery* dramatic postoperative improvement of myocardial function may occur

The severe alterations of myocardial function appear to be related to the degeneration of cardiac muscle fibers with development of interstitial fibrosis an apparently irreversible process These alterations may be enhanced in some cases by changes in myocardial architecture with sliding of fibers due to excessive distention of the LV In these cases the architectural myocardial abnormalities may regress with concomitant improvement of myocardial function following repair of the valvular defect and suppression of excessive distention

In an attempt to determine the future of myocardial function after valve replacement in patients with severe myocardial insufficiency the use of tests such as expansion and post extrasystolic potentiation[1] appears to be of interest

Clinical implications Patients with chronic AR often remain asymptomatic for a long time When the regurgitation is substantial this entails long standing mechanical overloading which eventually causes severe myocardial damage

Myocardial insufficiency increases the risk of both operative and late mortality and jeopardizes the chances for satisfactory long term results In some cases myocardial damage becomes irreversible but in others even apparently severe myocardial insufficiency may be reversed following complete suppression of mechanical overloading as evidenced by the improvement of myocardial function The time required to achieve such improvement is difficult to determine in the small number of patients of this series

Since there are no currently available criteria for predicting with certainty the course of myocardial lesions following surgery, myocardial insufficiency even when severe should not be considered a contraindication for surgery despite the significantly higher operative risk

Furthermore in the light of the results of this study it would not appear irrational to extend indications for surgery in severe AR to asymptomatic patients with severely impaired LVF ($EF \leq 40$ per cent and $\overline{VCF} \leq 0.60$ circ /sec) in the hope of avoiding irreversible myocardial damage

When the contractility of the myocardium is only moderately affected the decision is far more *difficult since nothing is known about the potential* activity of these alterations [1]

Serial echocardiographic investigations may contribute to the follow up of LVF in these patients provided their validity questioned by some is conclusively demonstrated

Summary

Hemodynamic and angiocardiographic analysis was performed prior to and 14 months on the

average following valve replacement in 11 patients with severe isolated pure chronic aortic regurgitation

The aortic diastolic pressure reduced prior to surgery reverted to normal as did the cardiac index. Left ventricular filling pressure elevated prior to surgery returned to normal while aortic systolic pressure did not vary substantially. The markedly increased stroke volume returned to normal as did the net left ventricular stroke work. Left ventricular end diastolic and end systolic volumes also markedly elevated decreased but did not return to normal levels.

The shape of the left ventricle which was more spherical than normal during end systole prior to surgery as evidenced by the decrease in the systolic axis ratio reverted to normal.

The ejection fraction severely reduced before surgery increased moderately (46 ± 13 vs 51 ± 19 per cent) as did the extent of circumferential fiber shortening (ΔD) (21 ± 8 vs 27 ± 12 per cent). The mean velocity of fiber shortening ($\overline{VCF}$) increased significantly (0.68 ± 0.2 vs 1.03 ± 0.47 circ/sec) as did the mean left ventricular ejection rate (1.32 ± 0.48 vs 1.91 ± 0.76).

Comparative analysis of the evolution of left ventricular function indices and of extramyocardial factors (end-diastolic fiber stretching and impedance to ejection) showed that whereas in some cases myocardial damage appeared to be irreversible in others dramatic improvement sometimes occurred following surgery. It was not possible however to determine the threshold below which the damage was irreversible.

It may therefore be concluded that in some patients with severe regurgitation attended by profound myocardial insufficiency correction of the valvular defect could produce not only clinical and hemodynamic improvement but also improvement in myocardial contractile status.

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Sequential changes of orthogonal electrocardiograms in progressive muscular dystrophy of the Duchenne type

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It has been generally found that myocardial involvement is frequently associated with progressive muscular dystrophy of the Duchenne type (PMD) but is relatively rare in other types of disorders Although much attention has been given to the increased value of the R/S ratio in Lead V and to the abnormal Q waves no clinical studies have yet analyzed the sequential changes of the R wave amplitude in orthogonal electrocardiograms and their relationship to the extent of cardiac involvement in PMD

The main purpose of the present study was thus to determine whether there is any relationship between sequential changes in the R wave amplitude and the severity of PMD

Materials and methods

Out of 84 patients with PMD 70 cases were selected who had been completely followed for a period of 2 years The patients were classified into eight stages from the mildest S(1) to the severest S(8) according to Swinyard Deaver s criteria This classification is based on the pattern ability and method of ambulation and on the degree of adequacy in activities of daily living The criteria for rating the eight stages of the patients functional ability were as follows

S(1) They ambulate with a waddling gait and marked lordosis Elevation activities are adequate They can climb stairs and curbs without assistance

S(2) They ambulate with a waddling gait and marked lordosis. Elevation activities are deficient They need support for curbs and stairs

S(3) They ambulate with a waddling gait and marked lordosis They cannot negotiate curbs or stairs but can achieve an erect posture from a standard height chair

S(4) They ambulate with a waddling gait and marked lordosis They cannot rise from a standard height chair

S(5) They are not dependent on a wheelchair and can perform all activities of daily living from a chair

S(6) They are dependent on a wheelchair They can roll the chair but require assistance in bed and other wheelchair activities

S(7) They are dependent on a wheelchair and need back support for good chair position.

S(8) They are restricted to bed They can perform no activities of daily living without maximum assistance

The validity of applying this classification to an evaluation of the cardiac status in this disorder has been justified in our previous echocardiographic studies by showing that the maximal diastolic endocardial velocity the ejection frac

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Table I Sequential changes in electrocardiographic and chest measurements

Case No	Age	Stage of Suinyard & Deaier A	B	Chest transverse diameter (TD) (cm) A	B	Chest sagittal diameter (SD) (c) A	B	TD/SD A	B	Rx A	B	Ry A	B	Rz A	B	Rx + Ry + Rz A	B	Q/Rz A	B
1	9	1	4	22 5	24 0	16 0	16 5	1 41	1 45	2 10	2 00	1 60	1.50	1 37	1.55	5 17	5 05	1 07	[illegible]
2	8	1	5	21 0	23 0	13 0	14 5	1 62	1 59	1 73	1 80	1 43	1 25	0 53	0 80	3 70	3 85	1.56	1c
3	7	1	3	21 0	22 0	15 5	14 0	1 35	1 57	2 13	1 65	1 88	1 65	0 93	1 83	4 95	5 13	1 39	116
4	7	1	2	20 0	20 5	15 0	14 5	1 33	1 41	3 30	2 75	1 70	1 65	1.55	1 95	6 55	6.35	1 45	1.3
mean	7 8	1	4	21 1	22 4	14 9	14 9	1 43	1 51	2 32	2 05	1 65	1 51	1 10	1 53	5 09	5 10	1 37	1.3
SD	0 9			1 0	1 5	1 3	1 1	0 13	0 09	0 68	0 49	0 19	0 19	0 49	0 52	1 17	1 02	0 71	0.3
p value (two sided sign test)				< 0 05		N S		N S		N S		< 0 05		< 0 10		N S		N.S	
5	8	2	4	—	22 0	—	12 5	—	1 76	1 77	0 85	2 09	1 84	0 97	2 05	5 82	4 74	0 66	0.
6	9	2	5	20 5	21 5	12 0	12 0	1 71	1 79	3 07	2 00	1 53	1 70	1 77	1 58	7.37	5 28	1 09	1.1
7	7	2	6	21 0	21 0	16 5	16 0	1 27	1.31	1 65	0 90	1 80	1 48	1 05	1 05	4.50	3 43	1 0⁷	1
8	7	2	4	22 5	25 0	15 5	17 5	1 45	1 43	1 73	1 38	1 60	1 65	0 85	0 88	4 18	3 90	1.38	1.
9	6	2	5	20 5	21 5	14 0	13 0	1 46	1 65	1 45	1 73	1 65	1 58	0 41	1 05	2 51	4 35	1 71	1.
mean	7 4	2	5	21 1	22 2	14 5	14.2	1 47	1 59	1 93	1 37	1 73	1 65	1 01	1 32	4 88	4 34	1 17	1
SD	1 1			1 0	1 6	2 0	2 4	0 18	0 21	0 65	0 50	0 22	0 14	0 49	0 49	1.83	0 72	0 40	0
p value (two sided sign test)				N S		N S		N S		< 0 05		N S		N S		N S		N.S	
10	14	3	5	—	24 0	—	14 0	—	1 71	1 20	0 68	1 75	1 18	0 98	1 40	3 93	3.25	2 10	1
11	7	3	6	22 5	24 0	16 0	15 5	1 41	1 55	0 85	0 40	1 85	1 35	0 60	0 58	3 30	2 33	1 25	1
12	9	3	5	24 0	26 5	16 0	18 0	1 50	1 47	2 53	1 65	2 60	2 65	1 27	1 43	6 40	5 73	1 37	1
13	6	3	5	20 5	20 5	16 5	15 0	1 24	1 37	1 73	1 35	1 00	1 15	0 53	1 13	3 27	3 63	1.38	1
14	10	3	5	21.5	23 5	14 0	14 5	1 54	1 62	2 20	1 39	1 96	1 85	0 37	0 65	4 53	3 89	2 73	2
mean	9 2	3	5	22 1	23 7	15 6	15 4	1 42	1 54	1 70	1 09	1 83	1 64	0 75	1 04	4 29	3 77	1 77	1
SD	3 1			1 5	2 1	1 1	1 6	0 13	0 13	0 69	0 53	0 57	0 63	0 37	0 40	1.29	1 25	0 64	0
p value (two sided sign test)				N S		N S		N S		< 0 005		N S		< 0 10		< 0 10		N S	
15	10	4	7	21 5	24 0	14 5	15 0	1 48	1 60	2 87	1 90	1 80	1 60	1 47	1 25	6 13	4 75	0 86	0
16	10	4	7	21 0	22 5	17 5	14 0	1 20	1 61	2 23	1 25	2 30	1 75	1 83	1 60	6 37	4 60	0 80	0.
17	12	4	7	24 0	25 0	15 0	14 5	1 60	1 72	2 37	1 65	2 07	1 78	1 53	1 78	5 97	5 20	1 13	1
18	9	4	6	21 0	22 5	14 0	14 5	1 50	1 55	2 27	2 15	1 67	2 22	1 03	1 10	4 97	5 47	1 48	1.
19	11	4	6	22 5	24 0	14 5	15 0	1 55	1 60	2 27	0 91	2 07	1 28	0 63	0 65	4 97	2 84	1 26	1
20	12	4	6	23 5	25 5	15 0	13 5	1 57	1 89	1 40	0 55	1 33	1 08	1 47	1 50	4 20	3 13	0 61	0
21	7	4	6	23 0	24 5	17 5	19 5	1 31	1 26	1 93	1 35	2 67	2.25	0.33	0 53	4 93	4 13	1 60	1
22	8	4	6	22 0	23 5	15 0	16 0	1 47	1 47	2.20	1 28	1 20	0 80	2 33	1 63	4 73	3 70	0 60	0
mean	9 9	4	6	22.3	23 9	15 4	15 3	1 46	1 59	2 19	1 38	1 89	1 60	1 33	1 26	5 28	4 23	1 04	1
SD	1 8			1 1	1 1	1 4	1 9	0 14	0 18	0 41	0 52	0 49	0 52	0 65	0 47	0 77	0 95	0 38	0
p value (two sided sign test)				< 0 001		N S		< 0 1		< 0 001		< 0 10		N S		< 0 005		< 0 10	
23	7	5	7	19 5	22 5	13 0	14 5	1 50	1 55	1 87	0 82	1 60	1 68	1 27	1 04	4 73	3 54	1.26	1
24	11	5	6	24 5	27 5	16 5	15 0	1 48	1 83	1 72	0 68	1 04	1 05	0 92	0 63	3 68	2.35	0 83	1 1
25	12	5	7	24 0	27 0	17 0	17 0	1 41	1 59	1 50	0 18	2 40	1 70	0 93	0 93	3 83	2 80	1 19	2.3
26	12	5	6	24 5	29 0	16 0	19 5	1 53	1 49	3 30	1 15	2 55	2 05	0 95	0 75	6 80	3 95	2 74	3 3
27	8	5	5	27 0	28 0	17 5	17.5	1.54	1 60	1 95	1 68	2 40	3 10	1 25	1 30	5 60	6 08	0 6⁹	0 5
28	14	5	6	22 5	24 5	18 0	17 5	1.25	1 40	0 60	0 50	2 20	2 50	1 00	1 38	3 80	4 13	2 37	1 6
29	10	5	6	22 5	25 0	17 0	17 5	1.32	1 43	1 95	0 80	1 00	0 55	0 70	0 55	3 65	1 90	2 57	1 8
30	11	5	7	21.5	24 0	14 5	15 0	1 48	1 60	1 44	0 68	0 58	0 85	0 90	1 05	2 92	2 58	1 69	0.8
31	10	5	7	23 0	24 0	15 0	14 5	1 53	1 66	2 57	1 43	2 00	1 55	1 37	1 48	5 93	4 45	1 22	0 9
32	16	5	6	27 0	?8 0	15 5	15 0	1 74	1 87	1 95	1 63	1 95	2 05	1 20	1 36	5 10	5 04	1.50	1 3
33	13	5	7	29 0	31 0	21 0	18 0	1 38	1 72	1 90	0 85	2 00	1 35	0 83	1 03	4 73	3 43	1 88	1.3
34	11	5	6	26 0	30 0	16 5	20 0	1 58	1 50	2 73	2 60	3 00	3 50	0 87	0 90	6 60	7 00	1 56	1.8
35	9	5	6	22 5	24 5	16 5	16 5	1 63	1 48	1 27	1 75	1 60	1 50	0 40	0 73	3 27	3 98	2.50	2 3
36	15	5	7	21 0	23 0	14 0	14 5	1.50	1 59	1 63	0 80	2 97	1 80	0 93	1 00	5 53	3 60	1 67	? 0

A = 1975 B = 1977 N.S = not signifi ant

ble I Cont d

Case No	Age	Stage of Swinyard & Deaver		Chest transverse diameter (TD) (cm)		Chest sagittal diameter (SD) (c)		TD/SD		Rx		Ry		Rz		Rx + Ry + Rz		Q/Rz	
		A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
37	11	5	7	25.5	26.0	18.0	15.0	1.42	1.73	1.60	0.53	2.27	2.10	0.87	1.48	4.73	4.10	1.46	1.24
38	12	5	6	21.5	23.5	17.0	15.5	1.26	1.52	2.07	0.58	2.33	1.25	0.33	1.18	4.73	3.00	2.00	1.13
39	15	5	5	25.0	26.0	14.5	15.0	1.72	1.73	1.03	0.25	2.63	2.75	0.87	1.92	4.53	4.92	1.35	1.12
40	13	5	8	22.5	25.0	17.0	14.5	1.32	1.72	1.17	0.90	1.90	1.65	1.10	0.80	4.17	3.35	0.52	0.88
41	11	5	7	21.5	23.0	15.5	12.5	1.39	1.84	2.40	0.70	2.10	1.85	1.03	1.50	5.53	4.05	1.29	1.20
42	13	5	6	22.5	23.5	16.0	16.5	1.41	1.42	1.60	0.55	1.80	1.60	1.50	1.50	4.90	3.65	1.02	0.77
43	11	5	7	22.0	23.0	17.5	15.0	1.26	1.53	1.23	0.78	1.53	1.15	0.73	1.35	3.50	3.38	1.91	1.67
44	11	5	5	23.5	25.5	15.5	15.5	1.52	1.65	1.27	0.95	1.73	1.55	1.60	1.00	4.60	3.50	1.31	1.75
45	12	5	6	23.0	25.0	15.5	13.0	1.48	1.9?	1.03	2.40	3.15	2.20	1.45	1.08	5.63	5.68	1.28	1.67
46	14	5	7	26.0	25.5	16.0	17.0	1.50	1.50	1.20	0.90	1.70	1.65	1.40	1.80	4.30	4.35	1.86	1.47
47	10	5	6	22.0	23.0	15.0	13.5	1.47	1.70	0.93	0.23	1.05	1.25	1.48	0.88	3.46	2.35	0.83	1.57
48	11	5	6	25.0	25.5	18.0	17.5	1.39	1.46	0.93	1.05	1.33	1.95	1.33	1.65	3.60	4.65	0.95	1.11
mean	11.7	5	7	23.6	25.5	16.3	15.9	1.46	1.62	1.65	0.96	1.95	1.75	1.05	1.13	4.61	3.83	1.52	1.49
SD	2.1			2.2	2.3	1.6	1.9	0.13	0.15	0.62	0.62	0.65	0.69	0.33	0.34	1.02	1.23	0.59	0.60
p value (two sided sign test)				< 0.001		N.S		< 0.001		< 0.001		< 0.05		N.S		< 0.001		N.S	
49	14	6	7	23.5	27.5	15.0	15.0	1.57	1.83	0.90	0.50	1.60	1.18	1.70	1.68	4.20	3.35	0.94	0.81
50	12	6	6	26.0	27.5	17.0	15.5	1.53	1.77	1.95	0.55	3.55	3.30	0.90	1.28	6.40	5.13	1.56	1.18
51	13	6	7	29.0	28.0	21.0	15.0	1.38	1.87	1.25	0.50	1.40	1.10	1.30	2.05	3.95	3.65	1.15	0.89
52	15	6	6	24.0	2.40	17.5	16.0	1.37	1.50	1.64	1.00	0.36	0.68	0.26	0.78	2.26	2.45	2.31	0.65
53	13	6	7	24.5	25.5	14.0	15.5	1.75	1.65	1.30	0.85	1.50	1.80	1.00	1.10	3.80	3.75	1.73	1.39
54	12	6	8	26.0	25.0	18.5	17.5	1.41	1.43	1.27	0	2.20	1.35	0.83	0.68	4.30	2.03	1.76	2.30
55	15	6	7	30.0	30.0	20.5	19.0	1.46	1.58	0.40	0.85	1.45	1.00	0.60	0.35	2.45	2.20	4.17	10.00
56	7	6	7	20.0	21.0	11.5	13.0	1.74	1.62	1.57	1.11	1.93	1.60	1.33	1.25	4.83	3.95	1.10	1.56
57	13	6	8	28.5	30.0	19.5	21.5	1.46	1.40	1.08	0.53	2.10	1.78	0.75	0.73	3.93	3.03	0.85	2.00
58	16	6	7	30.0	32.5	23.0	25.0	1.30	1.30	0.98	0.90	1.25	1.05	0.80	0.63	3.03	2.58	1.75	2.36
59	10	6	7	27.0	28.5	24.5	21.0	1.10	1.36	2.50	1.50	2.53	2.08	0.53	0.68	5.57	4.25	1.81	2.04
60	13	6	8	26.0	27.0	13.5	9.5	1.93	2.84	0.86	0.73	0.76	0.75	0.52	0.45	2.14	1.43	1.15	1.17
61	13	6	7	26.0	21.5	19.5	21.0	1.33	1.02	0.32	0.18	0.20	0.23	1.20	1.15	1.72	1.55	0.84	0.59
mean	12.8	6	7	26.2	26.8	18.1	17.3	1.49	1.63	1.23	0.67	1.60	1.38	0.90	0.99	3.74	3.03	1.63	2.07
SD	2.3			2.8	3.3	3.8	4.1	0.22	0.43	0.60	0.42	0.90	0.77	0.40	0.49	1.39	1.11	0.89	2.46
p value (two sided sign test)				N.S		N.S		N.S		< 0.01		< 0.05		N.S		< 0.005		N.S	
62	12	7	8	34.5	35.0	29.0	21.0	1.19	1.67	1.33	1.45	0.73	0.44	0.27	0.25	2.33	2.14	3.00	5.60
63	15	7	8	27.5	29.0	15.0	14.5	1.83	2.00	0.95	0.60	2.05	2.35	0.30	0.39	3.30	3.34	3.42	4.94
64	12	7	8	25.5	25.5	19.5	23.5	1.31	1.09	0.73	0.18	2.20	2.10	0.27	0.50	3.20	2.78	4.24	1.80
65	14	7	7	26.0	27.5	18.5	18.0	1.41	1.53	1.93	1.63	1.70	1.20	0.83	0.48	4.46	3.30	2.52	3.14
66	11	7	7	22.0	23.0	12.0	11.0	1.83	2.09	2.10	1.80	2.47	1.64	1.13	1.38	5.70	4.82	0.97	1.56
67	16	7	8	26.5	27.0	15.0	15.0	1.77	1.80	1.33	0.75	1.37	1.35	1.47	0.48	4.17	2.58	1.39	3.26
68	12	7	8	25.5	26.0	14.0	12.5	1.82	2.08	1.27	0.50	1.53	1.23	0.80	0.58	3.60	2.30	2.50	2.78
69	14	7	8	–	32.5	–	22.5	–	1.44	0.48	0.39	1.26	0.98	0.20	0.25	1.94	1.62	4.60	2.70
mean	13.3	7	8	26.8	28.2	17.6	17.3	1.59	1.71	1.27	0.91	1.66	1.41	1.02	0.54	3.59	2.86	2.83	3.22
SD	1.8			3.8	3.9	5.7	4.7	0.28	0.35	0.55	0.62	0.56	0.61	0.62	0.36	1.20	0.98	1.27	1.41
p value (two sided sign test)				< 0.05		N.S		N.S		< 0.01		< 0.10		N.S		< 0.01		N.S	
70	15	8	8	24.0	25.5	13.0	12.0	1.85	2.13	1.87	1.23	1.40	1.45	1.40	1.03	4.67	3.70	0.95	0.78
mean	11.2			23.9	25.3	16.4	15.9	1.48	1.62	1.65	1.06	1.80	1.60	0.99	1.09	4.43	3.75	1.61	1.72
SD	2.7			2.9	3.0	2.9	2.9	0.18	0.26	0.86	0.62	0.63	0.62	0.44	0.47	1.26	1.20	0.85	1.35
p value (two sided sign test)				< 0.001		N.S		< 0.001		< 0.01		< 0.01		N.S		< 0.01		N.S	

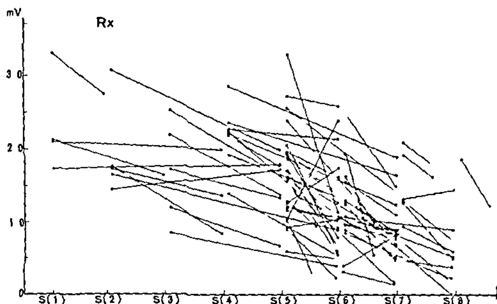


Fig 1 Sequential change in Rx amplitude The Rx amplitude tended to decrease with advances of Swinyard Deaver s stages

tion and the mean rate of circumferential fiber shortening tended to decrease with advance of Swinyard Deaver s stage

The numbers and mean ages of the patients in each stage are indicated in Table I

Scalar electrocardiograms (ECGs) were recorded with Frank s orthogonal lead system on a Mingograf 62 recorder at a frequency response of 0 1 to 1 200 Hz and a paper speed of 200 mm /sec Full details of the recording technique have been reported previously

Special attention was given to the location of the precordial electrodes Greatest difficulty was encountered in a patient with a marked chest deformity The position of electrode E was tentatively determined as the center of the precordium in the fourth intercostal space irrespective of the chest deformity The site of electrode M was determined on the back at the point opposite electrode E irrespective of the deformed spine After these two electrode positions had been determined the remaining electrodes were easily positioned according to the original Frank lead system

All ECG measurements were performed manually The details were as follows Measurements from scalar Leads X Y and Z included the amplitudes of P Q R S Q/R ratio and the T wave and the durations of the P and the QRS complex For all QRS measurements the PR segment served as baseline at the level of the QRS complex For the P wave the TP segment was used as baseline Maximal vectors for the QRS and T loops were determined in three pl projections–frontal left sagittal and horiz tal

Since respiration is the most important phy logical variable causing beat to beat variatio seven consecutive heart beats were selected fr each record in order to include at least respiratory cycle A mean value for each E measurement calculated from the seven conse tive beats was used for analysis

Determination of the abnormal Q wave based on the 96 percentile normal ranges The following criteria for the abnormal Q wave w then applied in this study

1 The Q wave amplitudes in Leads X Y an for subjects whose ages were from 5 to 9 yea were 0 4 mV 0 35 mV and 1 30 mV respecti ly and those for subjects aged above 10 yea were 0 32 mV 0 26 mV and 1 16 mV respecti ly

2 The Q/R ratio in Leads X Y and Z subjects whose ages were from 5 to 9 years we 0 29 0 22 and 1 09 respectively and those subjects aged above 10 years were 0 20 0 28 a 1 71 respectively

The chest transverse diameter (TD) che sagittal diameter (SD) and TD/SD ratio we measured in order to investigate the influence chest deformities on the ECG patterns

Results

Table I summarizes all pertinent data for th 70 patients As shown the amplitude of the

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

Table II Sequential changes in vectorcardiographic measurements maximal QRS vector

Case No	Age	Stage of Sunyard & Dealer		Frontal plane		Sagittal plane		Horizontal plane	
		A	B	A	B	A	B	A	B
1	9	1	4	2 93	2 50	1 86	2 13	2 29	1.96
2	8	1	5	2 29	2 19	1 39	1 80	1 93	1.80
3	7	1	3	3 00	2 09	2 00	2 13	2 43	2 13
4	7	1	2	4 07	–	2 57	–	3 57	–
mean	7 8	1	4	3 07	2 26	1 96	2 02	2 56	1.96
SD	0 9			0 74	0.21	0 94	0 19	0 71	0 17
p value (two sided sign test)				N S		N S		N S	
5	8	2	4	–	2 22	–	2 41	–	2.15
6	9	2	5	2 93	2 26	2 00	2.04	2 93	2 11
7	7	2	6	–	1 67	–	1 56	–	1 30
8	7	2	4	2 32	2 15	1 71	1 70	1 71	1.38
9	6	2	5	2 00	–	1 86	–	1 36	–
mean	7 4	2	5	2 42	2 08	1 86	1 93	2 00	1 74
SD	1 1			0 47	0 27	0 15	0 38	0 82	0 46
p value (two sided sign test)				N S		N S		N S	
10	14	3	5	–	1 20	–	2 69	–	2 59
11	7	3	6	–	1 39	–	1 39	–	0 93
12	9	3	5	3 00	2 76	2 07	2 76	2 36	1.51
13	6	3	5	2 00	1 77	1 14	1 51	1 75	1 64
14	10	3	5	2 71	2 31	1 89	2 10	2 14	1.55
mean	9 2	3	5	2 57	1 89	1 70	2 09	2 08	1 64
SD	3 1			0 51	0 65	0 49	0 64	0 31	0 60
p value (two sided sign test)				N S		N S		N S	
15	10	4	7	3 43	2 48	2 00	1 94	3 21	2 19
16	10	4	7	2 43	1 85	1 93	2 11	2 07	1 62
17	12	4	7	3 07	2 42	2 00	2 04	2 93	2 11
18	9	4	6	2 86	2 87	2 07	2 40	2 57	2 22
19	11	4	6	3 00	1 38	2 43	1 35	2 36	1.20
20	12	4	6	1 93	1 08	1 79	1 66	1 57	1 67
21	7	4	6	3 57	2 62	3 43	2 35	2 43	1 45
22	8	4	6	2 31	1 33	2 71	1 81	2 57	1 64
mean	9 9	4	7	2 83	2 01	2 30	1 96	2 46	1 76
SD	1 8			0 57	0 68	0 55	0 35	0 50	0 3[illegible]
p value (two sided sign test)				< 0 005		N S		< 0 005	
23	7	5	7	3 07	1 80	3 00	1 86	2 21	1.8[illegible]
24	11	5	6	1 79	1 11	1 14	1 06	1 82	0 75
25	12	5	7	2 71	1 78	2 29	2 24	1 57	2 [illegible]
26	12	5	6	3 86	–	3 14	–	3 43	–
27	8	5	5	–	3 44	–	3 26	–	2.03
28	14	5	6	2.36	2 59	2 36	2.67	2 29	2 30
29	10	5	6	2 21	0 85	1 79	1 22	2 07	1.2
30	11	5	7	1 32	0 91	1 29	1 43	1 50	1 19
31	10	5	7	2 86	1 74	2 00	2 14	2 07	1 7[illegible]
32	16	5	6	2 64	2 6[illegible]	1 71	2.22	2 14	2.1[illegible]
33	13	5	7	2 43	1 60	2 14	1 91	1 93	1 60
34	11	5	6	4 29	4 36	3 43	3 61	3 14	2 [illegible]5
35	9	5	6	2 07	–	2 00	–	1 54	–

A = 1975 B = 1977 N S = not significant

Table II Cont'd

Case No	Age	Stage of Swinyard & Deaver A	Stage of Swinyard & Deaver B	Frontal plane A	Frontal plane B	Sagittal plane A	Sagittal plane B	Horizontal plane A	Horizontal plane B
36	15	5	7	3.29	1.97	3.07	2.10	2.57	2.19
37	11	5	7	2.71	2.25	2.29	2.47	2.00	1.83
38	12	5	6	3.14	1.33	2.43	1.52	2.07	1.33
39	15	5	5	3.00	2.76	2.86	3.30	1.43	2.15
40	13	5	8	2.39	1.72	2.07	1.83	1.29	1.20
41	11	5	7	3.14	1.87	2.14	2.40	2.43	1.91
42	13	5	6	2.29	1.69	2.00	1.85	2.14	1.60
43	11	5	7	1.93	—	1.64	—	1.64	—
44	11	5	5	2.36	1.70	1.86	1.77	2.00	1.75
45	12	5	6	4.43	3.26	3.36	2.45	3.43	2.63
46	14	5	7	2.00	1.72	3.00	2.70	3.00	2.83
47	10	5	6	1.50	1.25	1.64	1.33	1.57	1.38
48	11	5	6	2.57	2.21	2.50	2.30	2.29	1.95
mean	11.7	5	7	2.65	2.02	2.29	2.16	2.15	1.85
SD	2.1			0.77	0.84	0.63	0.66	0.61	0.53
p value (two sided sign test)				< 0.001		< 0.10		< 0.005	
49	14	6	7	1.79	1.19	2.29	1.85	2.00	1.69
50	12	6	6	—	3.39	—	3.67	—	1.65
51	13	6	7	1.71	1.21	1.61	2.10	1.46	1.83
52	15	6	6	1.64	1.07	0.64	0.91	1.64	1.03
53	13	6	7	1.93	1.99	2.00	1.96	1.79	1.67
54	12	6	8	2.57	—	2.64	—	1.71	—
55	15	6	7	1.57	1.30	3.29	3.70	3.43	3.63
56	7	6	7	2.57	—	2.29	—	2.14	—
57	13	6	8	2.43	1.88	2.29	1.98	1.71	1.70
58	16	6	7	1.43	—	1.46	—	1.71	—
59	10	6	7	3.71	—	2.86	—	2.57	—
60	13	6	8	1.07	0.92	0.8[illegible]	0.87	1.07	0.90
61	13	6	7	0.64	0.64	1.25	1.15	1.36	1.30
mean	12.6	6	7	1.92	1.51	1.95	2.02	1.88	1.71
SD	2.3			0.81	0.82	0.81	1.05	0.62	0.79
p value (two sided sign test)				< 0.05		N.S		N.S	
62	12	7	8	1.43	1.54	1.07	1.47	1.46	1.83
63	15	7	8	2.25	2.34	2.29	2.41	1.29	1.96
64	12	7	8	2.39	2.25	2.43	2.14	1.29	1.08
65	14	7	7	2.64	2.07	2.29	1.37	2.43	1.70
66	11	7	7	3.14	2.44	2.43	2.31	2.14	2.55
67	16	7	8	2.00	1.39	2.29	1.89	2.50	1.72
68	12	7	8	2.00	—	1.64	—	1.43	—
69	14	7	8	1.71	0.98	1.43	1.06	1.07	0.81
mean	13.3		8	2.13	1.85	1.98	1.81	1.70	1.66
SD	1.8			0.62	0.55	0.53	0.52	1.56	0.57
p value (two sided sign test)				< 0.1		N.S		N.S	
70	15	8	8	2.43	—	1.57	—	2.29	—
mean	11.2			2.48	1.93	2.10	2.04	2.10	1.78
SD	2.7			0.77	0.72	0.63	0.64	0.61	0.53
p value (two sided sign test)				< 0.001		< 0.1		< 0.001	

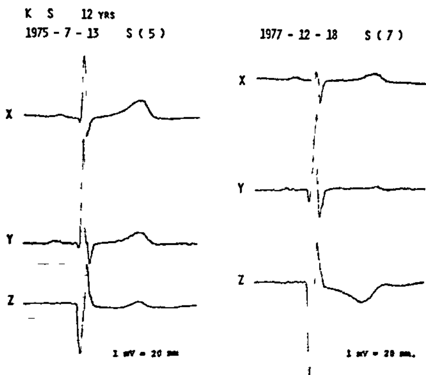


Fig 3 Representative scalar ECGs obtained from a patient whose stage advanced from S(5) in 1975 to S(7) in 1977 The amplitudes of Rx and Ry decreased in 1977 respectively On the other hand Qz increased from 1 15 mV to 2 30 mV

Discussion

The most prominent sequential ECG change in PMD was a progressive reduction in the magnitude of the leftward QRS force which was reflected by a decrease in the magnitudes of Rx of the leftward force in the horizontal plane and of the maximal QRS vector in the frontal plane It appeared reasonable to speculate that chest deformities which are observed in almost all cases in the moderate and advanced stages might shift the heart to the right side with a possible resultant decrease in the leftward QRS force Indeed TD and the TD/SD ratio tended to increase with advancing clinical severity However it was shown in a previous study[7] that an increase in TD led to an increase in the Rx amplitude not a decrease in Rx and that the TD/SD ratio did not influence the Rx amplitude Furthermore close inspection of each subject indicated that there may be no direct correlation between the reduction of the Rx amplitude and the degree of chest deformity Heymsfield and colleagues were unable to ascribe ECG changes in PMD to pectus excavatum which is frequently associated with this disorder Thus it would appear that the chest deformities may not be the main determinant of the reduction of the leftward QRS force although they might be partially involved Sanyal and associates revealed that progression of the disease would tend to be associated with myofibrillar loss of the left ventricular wall which could account for a significant reduction in the leftward QRS force Frankel and Rosser[11] demonstrated that in patients with this disorder histologic evidence of degenerative changes appeared initially in the posterobasal segment of the left ventricle subsequently spread to involve the outer third of the left ventricular free wall and finally manifested itself as diffuse transmural fibrosis Their observations may substantiate our findings that an anterior shift of the QRS forces (deep Qz or large Q/Rz) appeared in the early stages and subsequently the leftward QRS force decreased with progression of the disorder In our present state of knowledge it seems justified to infer from these results that the decrease in the leftward QRS force might result mainly from myofibrillar loss of the left ventricular free wall and that a progressive reduction of the Rx amplitude should be of predictive value in the assessment of the extent of cardiac involvement

It was also demonstrated in a previous report from our laboratory that if the number of high

frequency components of the QRS complex in the combined three leads exceeded nine this was strictly indicative of a more advanced stage than S(5) and that on the other hand the number of high frequency components tended to decrease in the most severely affected patients encountered in S(7) and S(8) especially those who experienced congestive heart failure In an assessment of the extent of cardiac involvement in PMD our previous echocardiographic studies revealed that left ventricular functions tended to be depressed with advancing clinical severity

A distinctive ECG pattern consisting of tall R waves in Leads V_1 aV_L V_5 and V has consistently been reported in 80 to 90 per cent of patients with PMD The anterior shift of the QRS force is reflected by a tall R wave in Lead V_1 of the standard 12 lead system and by a deep Q wave in Lead Z of the Frank lead system In this study the frequency of observation of abnormal Q waves in any one of the three leads was 93 per cent in the 70 cases This finding is consistent with previous reports

The pathogenesis of the abnormal Q wave remains undetermined although at present it seems most likely that replacement of normal cardiac tissue by fibrosis with lateral extension of scarring may explain the presence of Q waves It should be pointed out that the occurrence of deep Q waves was found to be quite high even in the early stages of PMD and that it did not bear a direct relation to the sequential evolution of the disorder Thus although the presence of a large Q wave in the early stages represents a useful ECG sign for the early detection of PMD it has only limited value in assessing the extent of cardiac involvement

Recently Heymsfield and associates made an extensive study of the sequence of cardiac changes in PMD They pointed out that a tall R wave in Lead V_1 and a deep Q wave in Leads I II or V_5 are frequently observed both in patients with early PMD and those with late PMD Their observations are thus in agreement with the present findings

Although the exact pathogenesis of our ECG findings cannot be clearly defined certain conclusions can be drawn from this study as follows

1 The leftward QRS force progressively decreased with advancing clinical severity and can be used as an index of the extent of cardiac involvement

2 An abnormal Q wave was frequently observed in each stage and the occurrence of abnormal Q waves did not increase with the progression of PMD

3 The presence of a deep Q wave was not suitable as an index for the assessment of the cardiac involvement

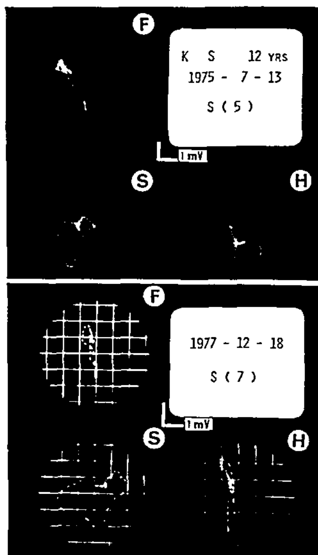


Fig 4 Representative vectorcardiograms recorded from the same patient as in *Fig 3* The magnitude of the maximal QRS vector in the frontal plane decreased from 2 71 mV in 1975 to 1 78 mV in 1977 In the horizontal plane the QRS loop became elongated with its long axis in the anteroposterior direction in 1977 In the sagittal plane the anterior force was markedly augmented in 1977

Summary

Sequential changes of orthogonal electrocardiograms in 70 patients with progressive dystrophy of the Duchenne type (PMD) were investigated The patients were classified into eight stages from the mildest S(1) to the severest S(8)

Table III Incidences of the Q wave and Q/R ratios above the 96 percentile normal ranges

Stage of Swinyard & Deaver	No of subjects	X lead Q A	X lead Q B	X lead Q/R A	X lead Q/R B	Y lead Q A	Y lead Q B	Y lead Q/R A	Y lead Q/R B	Z lead Q A	Z lead Q B	Z lead Q/R A	Z lead Q/R B	X Y Z leads A Q	X Y Z leads A Q/R	X Y Z leads A Q or Q/R	X Y Z leads B Q	X Y Z leads B Q/R	X Y Z leads B [illegible]
S (1)	4	3 (75%)	2 (50%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (50%)	4 (100%)	3 (75%)	4 (100%)	3 (75%)	3 (75%)	4 (100%)	4 (100%)	4 (100%)	[illegible]
S (2)	5	2 (40%)	2 (40%)	1 (20%)	2 (40%)	1 (20%)	0 (0%)	1 (20%)	0 (0%)	2 (40%)	2 (40%)	3 (60%)	5 (100%)	4 (80%)	4 (80%)	5 (100%)	4 (80%)	4 (80%)	[illegible]
S (3)	5	2 (40%)	2 (40%)	2 (40%)	2 (40%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (40%)	4 (80%)	5 (100%)	4 (80%)	3 (60%)	5 (100%)	5 (100%)	4 (80%)	4 (80%)	[illegible]
S (4)	8	5 (63%)	3 (38%)	0 (0%)	3 (38%)	2 (25%)	2 (25%)	1 (13%)	3 (38%)	4 (50%)	3 (38%)	5 (63%)	4 (50%)	7 (88%)	4 (80%)	7 (88%)	6 (75%)	5 (63%)	[illegible]
S (5)	26	10 (38%)	8 (31%)	6 (23%)	12 (46%)	4 (15%)	6 (23%)	2 (8%)	3 (12%)	16 (62%)	20 (77%)	20 (77%)	21 (81%)	18 (69%)	22 (85%)	23 (88%)	21 (81%)	23 (88%)	[illegible]
S (6)	13	4 (31%)	4 (31%)	4 (31%)	7 (54%)	4 (31%)	2 (15%)	4 (31%)	2 (15%)	9 (70%)	10 (77%)	10 (77%)	9 (70%)	11 (85%)	13 (100%)	13 (100%)	11 (85%)	13 (100%)	[illegible]
S (7)	8	0 (0%)	1 (13%)	3 (38%)	3 (38%)	1 (13%)	3 (38%)	1 (13%)	1 (13%)	3 (38%)	6 (75%)	7 (88%)	8 (100%)	4 (50%)	7 (88%)	7 (88%)	8 (100%)	8 (100%)	[illegible]
S (8)	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	[illegible]
Total	70	26 (37%)	22 (31%)	16 (23%)	29 (41%)	12 (17%)	13 (19%)	9 (13%)	9 (13%)	39 (56%)	49 (70%)	53 (76%)	55 (79%)	51 (73%)	58 (83%)	65 (93%)	58 (83%)	61 (87%)	[illegible]

A = 1975 B = 1977

according to Swinyard Deaver's criteria The most prominent finding was a progressive reduction in R wave amplitude in Lead X (Rx) with advancing severity It was considered that loss of electrical activity in the left ventricular free wall might be mainly responsible for the reduction in the Rx amplitude An abnormal Q wave was frequently observed in each stage Its occurrence remained essentially unchanged with the progression of PMD Thus the presence of a deep Q wave cannot serve as an index for assessing the heart involvement but rather we conclude that a reduction of the Rx amplitude can be a useful criterion for estimating the extent of cardiac involvement in PMD

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\bdulmassıh S Iskandrıan M D
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Complete occlusıon of the left maın coronary artery ıs rare and has a varyıng clınıcal presentatıon It has been assocıated wıth congenıtal atresıa of the left coronary ostıum[1] syphılıtıc coronary osteal occlusıon[2,3] congenıtal fusıon of the left coronary cusp to the aortıc wall[4] followıng aortıc valve replacement[5] and secondary to atherosclerosıs[6-8] Thıs report revıews the clınıcal hemodynamıc and angıographıc fındıngs ın three patıents wıth atherosclerotıc complete occlusıon of the left maın coronary artery as documented by cıneangıography

Case No 1 A 6? year-old whıte man a physıcıan wıth a ten year hıstory of classıc angına pectorıs developed an ıncrease ın frequency and duratıon of angına over a perıod of three months He had a past hıstory of three myocardıal ınfarctıons, cıgarette smokıng and hypertensıon Hıs medıcatıons ıncluded propranolol (80 mg /day) dıgoxın hydrochlorothıazıde and nıtroglycerın Physıcal examınatıon revealed a blood pressure of 140/70 mm Hg Bılateral carotıd bruıts were present Cardıac examınatıon was normal. The electrocardıogram showed poor R wave progressıon ın Leads V to V wıth non specıfıc ST T wave changes The serum cholesterol was 262 mg per cent and the serum trıglycerıdes were 131 mg per cent

At cardıac catheterızatıon the cardıac ındex was 3 1 L./mın /M and the left ventrıcular end-dıastolıc pressure was 6 mm. Hg. Left ventrıculography demonstrated the left ventrıcle to be mıldly enlarged wıth mıld dıffuse hypokınesıs. The ejectıon fractıon was 0.52. Selectıve coronary arterıography showed total occlusıon of the left maın coronary artery just dıstal to ıts orıgın (Fıg 1) However durıng selectıve rıght coronary arterıography both the left anterıor descendıng and left cırcumflex coronary arterıes were vısualızed vıa rıch rıght to-left collaterals. The rıght coronary artery was narrowed 90 to 95 per cent at ıts mıdportıon (Fıg 2)

Followıng catheterızatıon the patıent was entırely asymptomatıc However sıx days later whıle awaıtıng bypass surgery the patıent experıenced crushıng chest paın and sustaıned a cardıac arrest Resuscıtatıon was unsuccessful. At autopsy the heart weıghed 600 gms and the left ventrıcular wall measured 1.8 cm The left maın coronary artery was completely occluded just dıstal to ıts orıgın. Cross-sectıons of the left maın coronary artery revealed complete oblıteratıon of the lumen wıth calcıfıc atherosclerotıc degeneratıon The left anterıor descendıng and left cırcumflex coronary arterıes contaıned atherosclerotıc plaques but the lumens of these vessels were less than 50 per cent narrowed ın cross-sectıonal area. The rıght coronary artery had segmental narrowıng as descrıbed above There was coagulatıve necrosıs of the septum and posterıor wall wıth polymorphonuclear leukocyte ınfıltratıon consıstent wıth recent myocardıal ınfarctıon and a 2 cm area of old healed ınfarctıon at the anteroseptal portıon of the ventrı le

Case No 2 A 52 year-old whıte woman wıth a ten year hıstory of stable effort ınduced angına pectorıs, had recently notıced an ıncrease ın frequency and duratıon of the angına despıte medıcal therapy whıch ıncluded propranolol (160 (mg /day) ısosorbıde dınıtrıte and nıtroglycerın. She had a past hıstory of hypertensıon and type II hyperlıpıdemıa On examınatıon the blood pressure was 120/75 mm Hg and the pulse was ?2 per mınute Cardıac examınatıon revealed a Grade II/VI early systolıc ejectıon murmur at the left sternal border No gallops were present The chest x ray demonstrated calcıfıcatıon of the aortıc knob wıthout cardıomegaly The electrocardıogram had non-specıfıc dıffuse ST T wave changes.

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Fig 1 Selective left coronary arteriography in patient No 1 in the shallow left anterior oblique projection showing total occlusion of the left main coronary artery just distal to its origin and failure to opacify the left coronary system

At cardiac catheterization the cardiac index was 2 9 L/min/M and the left ventricular end-diastolic pressure was 25 mm Hg The left ventricle was mildly enlarged with mild diffuse hypokinesis and the ejection fraction was 0 56 Minimal mitral regurgitation was present Selective coronary arteriography revealed a totally occluded left main coronary artery just distal to its origin The right coronary artery was narrowed 50% at its midportion Rich right to left collateralization visualized both the left anterior descending and left circumflex coronary arteries (Fig 3) Two days following catheterization the patient underwent saphenous vein bypass surgery to the left anterior descending left circumflex and right coronary arteries She has remained asymptomatic over a six month follow up period

Case No 3 A 4_ year old white man with a one year history of classic angina pectoris had recently noticed a marked reduction in exercise tolerance and an increase in frequency and duration of angina over a period of six months He had a past history of a myocardial infarction and cigar tte smoking His medications included propranolol (80 mg/day) and nitroglycerin On examination the blood pressure was 110/70 mm Hg and the pulse was 72 per minute The physical examination was entirely normal All laboratory studies were also normal The electrocardiogram showed first degree A V block with non specific ST T wave changes in Leads I and aV

At cardiac catheterization the cardiac index was 3 9 L/min/M and the left ventricular end diastolic pressure was 11 mm Hg Left ventriculography demonstrated a moderately enlarged left ventricle with moderate anterior hypokinesis The ejection fraction was 0 54 Selective coronary arteriography revealed complete occlusion of the left main coronary artery two mm distal to its origin The right coronary artery was large dominant and mildly irregular throughout Both the left anterior descending and left circumflex coronary arteries were opacified via right to left collaterals Three days following catheterization the patient underwent double saphenous vein bypass surgery to the left anterior descending and left circumflex coronary arteries The hospital course was uncomplicated and the patient has remained asymptomatic over a six month follow up period.

Discussion

Significant narrowing of the left main coronary artery is infrequent occuring in approximately per cent of patients with coronary artery disease[9,10] Moreover, 96 per cent of patients with left main coronary artery involvement have associated disease of the other three major vessels However complete occlusion of the left main coronary artery is extremely rare In the past ten years at Hahnemann Medical College and Hospital 7 000 coronary arteriograms have been performed only three patients were noted to have complete occlusion of the left main coronary artery (incidence of 0 042 per cent) Similarly Frye and associates[7] found atherosclerotic complete occlusion of the left main coronary artery in only four patients among 6 000 patients studied by angiography (incidence of 0 067%) Goldberg and colleagues[6] have collected only six patients with total left main occlusion from two institutions during a seven year period[6]

When the left main coronary artery is not visualized by selective cineangiography an anomalous origin of this vessel should be considered either from the right sinus of Valsalva or from the proximal right coronary artery[12] In our three cases both the left anterior descending and left circumflex coronary arteries were visualized via extensive collateral vessels from the right coronary artery Moreover the portion of the left main coronary artery proximal to the obstruction was visualized by selective cineangiography

Although the importance of collateral circulation in patients with coronary artery disease has been the subject of much dispute[13-15] we believe that in this subset of patients with total occlusion of the left main coronary artery the collateral vessels have a functional role both in the survival of the patients and in maintaining the global function of the left ventricle In two recent reports of total occlusion of the left main coronary artery a similar conclusion was reached However the crescendo pattern of angina in our



Fig 2 Selective right coronary arteriogram in the shallow left anterior oblique projection in patient No 1 There is a high grade lesion in the midportion of the right coronary artery and rich collaterals opacifying the distal left anterior descending coronary artery seen in the right hand corner of the figure

three patients suggests that the coronary blood flow through collaterals was not adequate to meet the myocardial oxygen requirement and this has been borne out by the findings of a number of other investigators

Although angiographic assessment of the left anterior descending and the left circumflex coronary arteries may be difficult since they are visualized solely via collateral flow we suggest that patients with left main occlusion should be considered candidates for direct revascularization procedures in the presence of reasonable left ventricular function Moreover if such patients continue to have an unstable pattern of angina pectoris following catheterization despite optimal medical therapy then preoperative intra aortic balloon counterpulsation should be considered The death of one of our patients while awaiting surgery despite being asymptomatic suggests that surgery should not be unduely delayed The other two patients in our study who underwent saphenous vein bypass surgery are completely asymptomatic six months following the operation



Fig 3 Selective right coronary arteriogram in the shallow right anterior oblique projection in patient No 2 There are rich collaterals opacifying the left coronary artery system The left coronary artery was totally occluded in this patient See text for details

Summary

In this report we describe the clinical hemodynamic and angiographic findings in three patients with atherosclerotic complete occlusion of the left main coronary artery This rare entity was only seen in three out of 7000 coronary angiograms The three patients had extensive right to left collateralization Two patients underwent saphenous vein bypass surgery and are asymptomatic while the third patient died awaiting surgery We suggest that patients with complete left main occlusion must undergo surgery as soon as possible

Addendum

Since the submission of this manuscript for publication we have seen two additional patients with complete occlusion of the left main coronary artery The first patient presented with angina pectoris of recent onset with normal left ventric ular contraction pattern and normal ejection fraction and selective coronary arteriography demonstrated total occlusion of the left main coronary artery just distal to its origin The second patient presented with exacerbation of longstanding angina and the left ventricular contraction pattern was depressed with akinesia of the anterior wall. On selective coronary arteri ography the left main coronary artery had an anomalous origin from the right sinus of Valsalva and was totally occluded 1 cm from its origin Both patients had rich right to left collaterals and in both the coronary artery disease was limited to the left main coronary artery Both patients are asymptomatic following saphenous vein bypass surgery

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Aortico—left ventricular tunnel

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Abnormal communication between the aorta and the left ventricle was first recognized at the turn of the century by Hart.[1] He described delayed rupture of a congenital aneurysm of the right sinus of Valsalva into the left ventricle in adults. Edwards[2] in 1961 described the case of an 18-month-old child with a saccular aneurysm of the ascending aorta communicating with the left ventricle. This was the first reported case of this abnormality in children. During the ensuing years cases similar to that described by Edwards were observed and led to introduction of the term "aortico-left ventricular tunnel" by Levy and associates[3] in 1963. This new entity, different from the previously recognized rupture of the sinus of Valsalva, was defined as an abnormal congential communication between the root of the aorta and the left ventricle that bypassed the aortic valve and resulted in aortic regurgitation. Twenty-one cases have been reported to date.[4] The rarity of this malformation, the interesting clinical presentation, and the associated abnormalities prompted us to report an additional case and to review the literature.

Case report

A seven-month-old boy was referred to the Texas Heart Institute in 1974 for evaluation of a heart murmur that had been discovered at birth. The patient was born after normal gestation without complications or drug ingestion by the mother. He did not suffer respiratory infections or cyanosis. Development of the child was normal and no symptoms were apparent. No other family members had congenital heart disease.

Upon physical examination, the patient was a healthy-appearing boy whose height was 64.8 cm. and whose weight was 8,518 Gm. The blood pressure was 100/50 mm. Hg and the heart rate was 138 beats per minute. The heart was enlarged and there was a diffuse impulse over the left precordial area. The second heart sound was obscured by a Grade 4/6 "to-and-fro" systolic-diastolic murmur heard maximally along the left upper sternal border. Neither ejection clicks nor gallop sounds were heard. All peripheral pulses were symmetrical with bounding quality. There were no physical signs of congestive heart failure.

The blood hematocrit was 35.6 volume per cent, hemoglobin was 11.7 grams per cent. The left ventricle appeared enlarged and a prominent vascular structure in the right superior mediastinum was seen on chest roentgenogram. The lung fields were clear without evidence of heart failure. Electrocardiogram showed a sinus rhythm, QRS axis of 30 degrees, and evidence of left ventricular hypertrophy.

When cardiac catheterization was done, a wide pulse pressure was found in the aorta, but there was no valvular gradient (Table I). Contrast media introduced into the left ventricle filled the aorta via two separate channels, one through the aortic valve and the other through a separate tunnel that arose anteriorly and superiorly from the left ventricle and communicated with the ascending aorta, passing around the aortic valve (Fig. 1). The dye moved within the tunnel in a to-and-fro fashion during the cardiac cycle. Three separate aortic leaflets were easily identified. The entire ascending aorta was notably dilated. Injection into the right ventricle showed no outflow tract abnormality. There was no intracardiac shunt.

Since the patient was asymptomatic and the surgical experience in correcting this malformation was limited, we elected to defer the operation until the patient doubled his weight. During the interim of 32 months he remained asymptomatic and developed normally. He was recently readmitted to this hospital. Repeat cardiac catheterization showed no hemodynamic changes. At the time of operation, a large arterial-like structure 1.5 cm. in diameter was attached to the

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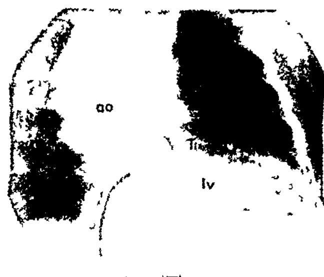


Fig 1 Left ventricular angiogram shows a large left ventricular cavity *(lv)* dilated ascending aorta *(ao)* and the tunnel *(T)* connecting the left ventricle to the aorta

Table I Hemodynamic data of the patient with aortico-left ventricular tunnel

Site	*Pressure*	*(mm Hg)*	*O saturation (%)*
Superior vena cava	–	–	65
Inferior vena cava	–	–	75
Right atrium	–	$\overline{4}$	81
Right ventricle	22/0	–	67
Pulmonary artery	22/10	$\overline{17}$	68
Left ventricle	10_/0 8	–	93
Aorta	105/40	$\overline{68}$	93
Left atrium	–	$\overline{8}$	95

aorta in an end to side fashion (Fig 2) The proximal portion of the tunnel was embedded in the left ventricle The gross appearance of the tunnel was similar to the aorta The aortic valve and orifice of the tunnel were inspected (Fig 3) The aortic valve was tricuspid with slightly thickened leaflets The extracardiac portion of the tunnel was resected and ligated Microscopic examination of this section showed three layers consisting of intima elastic media and adventitia The outer half of the elastic media was organized in an orderly manner similar to that of the aorta while the inner half became disorganized (Fig 4) Atheromatous plaques were scattered along the intimal surface (Fig 5) There was no cystic medial degeneration and the content of mucopolysaccharide was normal Histologically the tunnel resembled a large artery with atherosclerosis The postoperative course was smooth A soft 2/6 aortic regurgitation murmur became evident several days after surgery The patient was discharged eight days after operation

Discussion

Aortico-left ventricular tunnel is a rare congenital anomaly perhaps even rarer than



Fig 2 Anatomical relationship between the tunnel and the aorta viewed at the time of surgery The tunnel *(T)* appears as an arterial like structure connecting the left ventricle *(LV)* to the aorta *(AO)* in the end to side fashion

congenital aortic regurgitation and congenital aneurysm of the sinus of Valsalva Levine and Harvey[15] indicated that in their 600 patients with aortic regurgitation only two were considered congenital Before 1961 90 cases of congenital aneurysm of the sinus of Valsalva were reported[1] but only 22 cases of aortico-left ventricular tunnel have been described thus far More males than females were reported with the ratio of 13 to 8 and there was one case of unreported sex Among these 22 cases 20 were available for detailed clinical analysis (Table II)

Clinically all 20 patients had a heart murmur that was detected by age two years The murmur described at birth in 11 patients always had systolic and diastolic components mimicking the murmur of aortic insufficiency and was best heard along the left sternal border Ejection clicks were present in several patients Peripheral pulses in general were full and bounding in quality Not infrequently isolated aortic valvular



Fig 3 Inspection of the aortic valve and the tunnel after transecting the ascending aorta shows the orifice of the tunnel *(T)* to be smooth and the aortic valve *(AV)* was tricuspid and slightly thickened

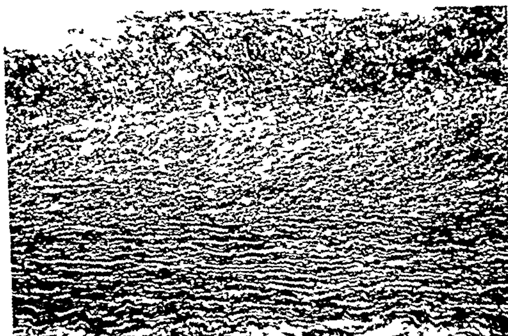


Fig 4 Microscopic examination of the tunnel shows its elastic media has the structure of an elastic artery with preservation of the orderly lamellar arrangement peripherally *(bottom)* but fragmented and disorderly internally *(top)* (VVG stain original magnification ×200)

insufficiency was suspected before the correct diagnosis was established with the aid of cardiac catheterization or autopsy findings Symptoms of congestive heart failure developed before the end of the first year of life in all but four patients who remained asymptomatic Four patients developed severe congestive heart failure shortly after birth Whether the onset of heart failure bears any prognostic value remains to be analyzed Abnormalities of chest roentgenogram were mentioned in 19 patients and all had cardiomegaly with dilatation of the ascending aorta Seventeen



Fig 5 The tunnel histologically resembles a large artery with elongated broad acellular plaques lying on the intimal surface and localized disruption of the internal elastic membrane (VVC stain original magnification ×125)

patients had left ventricular hypertrophy with ST T changes evident on the electrocardiogram Only one patient had a normal electrocardiogram

Among the 22 patients 19 underwent cardiac catheterization The diagnosis of aortico-left ventricular tunnel was based upon catheterization data in 11 In the other eight patients, the diagnosis was not clear until operation or autopsy Hemodynamically five patients had evidence of aortic stenosis and five had a gradient across the right ventricular outflow tract The aortic valve was abnormal in 45 per cent of all reported cases three had a bicuspid aortic valve six had a thickened tricuspid aortic valve, and one had a dome shaped tricuspid aortic valve evident angiographically during systole Associated anomalies were reported in four patients one with pulmonic stenosis one with patent ductus arteriosus and possibly pulmonic stenosis one with patent ductus arteriosus and a patent foramen ovale[9] and one with an absent right coronary artery[11]

Anatomically the orifice of the tunnel was just above or at the level of the right coronary sinus and did not bear definite relationship to the aortic cusps The tunnel ran through the anterior wall and ventricular septum behind the right ventricular outflow tract and entered the left ventricle high in the septum just beneath the annulus of the aortic valve Both orifices were smooth in appearance Displacement of the septum anteriorly created right ventricular outflow obstruction in five patients Aneurysmal dilatation of the aortic root was found in all patients and could compress the left coronary artery as shown by Edwards[2] Hypertrophy of the left ventricular wall and dilatation of the left ventricular cavity also were present

Histologically however the reported findings have not been completely consistent Levy and co workers[1] reported that elastic fibers of the media of the aorta were present in the tunnel wall up to its passage through the ventricular septum From that point the tunnel wall showed nonspecific hyalinized collagen resembling a myocardial sinusoid This finding was interpreted as consistent with the concept that the tunnel was an anomalous coronary artery entering the left ventricle through a myocardial sinusoid Cooley and colleagues also observed the presence of elastic media in the tunnel However a large amount of acid mucopolysaccharide contained in cyst like spaces within the elastic media also was found and led to the interesting hypothesis that medial cystic necrosis might be the pathogenesis of the tunnel Robert and Morrow[8] conversely

Table II Summary of reported cases of aortico-left ventricular tunnel

Case	Author	Age operated or died	Sex	Onset murmur	Onset CHF	Cardiac catheterization	Operation	Pathological findings	Result
1	Levy	5 yr	M	1 wk	Infancy	LV = 175/0 Ao = 105/65	yes	AS bicuspid AV PS RV outflow obstruction	Died
2	Levy	10 yr	M	1 day	Infancy		yes	Tricuspid AV	Alive
3	Levy	3 yr	M	9 mo	Infancy		yes	Tricuspid AV	Alive
4	Morgan	16 day	M	Birth	Birth	Slight mitral insufficiency	no	Malformed tricuspid AV	Died
5	Cooley	16 mo	M	Birth	7 mo	LV = 129/0-13 Ao = 107/56 RV = 28/9 PA = 21/15	yes	AS irregular tricuspid AV PDA PS? RV outflow obstruction	Died
6	Roberts	14 yr	M	3 mo	Asymp	HiRV = 22/1 LoRV = 1[illegible]0/4	no	AS bicuspid AV RV outflow obstruction	Died
7	Bove	4 yr	F	8 wk	7 mo		no	Tricuspid AV RV outflow obstruction	Died
8	Bove	2 ½ yr	M	Birth	5 wk	RV = 13/0 PA = 11/7	yes	Bicuspid AV	Alive
9	Bove	3 day	M	Birth	2 day		no	Thick tricuspid AV RV outflow obstruction	Died
10	Bernhard	2 yr	M	Birth	8 day		yes	Thick tricuspid AV	Alive Mild AI
11	Fishbone	11 yr	F	3 mo	Asymp	LV = 105/9 Ao = 104/70	yes	Tricuspid AV dome shape in systole	Alive Mild AI
12	Perez Martinez	13 mo	M	Birth	10 mo	LV = 100/8-14 Ao = 100/30	yes	Tricuspid AV	Died
13	Somerville	5 yr		Birth		1 c̄ ΔAV = 5 mm Hg	yes	2 c̄ AS	All alive
14	Somerville	6 yr	2M	3 wk	< 6 yr		yes	All c̄ tricuspid AV	2 c̄ AI
15	Somerville	7 yr	1F	2 yr		1 c̄ ΔAV = 18 mm Hg	yes	1 c̄ absent RCA 1 c̄ thick AV	
16	Somerville	?16 yr	F				yes		Died 8 yrs later AI
17	Mair	9 mo	F	Birth	2 day	LV = 99/10 15 Ao = 97/37	yes	Thick tricuspid AV	Alive Mild AI
18	Okoroma	?3 yr	F	4 day	3 yr		yes	Tricuspid AV	Alive Mild AI
19	Okoroma	2 yr	F	Birth	Birth		yes	Tricuspid AV	Alive Mild AI
20	Nichols	5 mo	F	15 day	Asymp	LV = 100/9	yes		Alive Mild AI
21	Edwards	18 mo	?				no	Compressed LCA tricuspid AV	Died
22	Present report	3 yr	M	Birth	Asymp	LV = 105/0 8 Ao = 105/40 RV = 22/0 PA = 22/10	yes	Thick tricuspid AV	Alive Mild AI

Ao = aorta AI = aortic insufficiency ΔAV = gradient between aorta and left ventricle AS = aortic stenosis AV = aortic valve CHF = congestive heart failure HiRV = high right ventricle LoRV = low right ventricle LCA = left coronary artery LV = left ventricle PA = pulmonary artery PDA = patent ductus arteriosus PS = pulmonic stenosis RCA = right coronary artery RV = right ventricle

did not detect an excessive amount of mucopoly saccharide within the elastic media nor did the tunnel resemble a blood vessel in composition Morgan and Mazur[4] in examining the tissue of the common wall between the pulmonary artery and the aortico ventricular fistula noticed a defect in the formation of the fibrous skeleton of the heart with apparent separation of the aortic annulus from the remaining portion of the common wall They postulated that turbulent flow of blood in this attenuated area resulted in the communication between the aorta and left ventricle Bove and Schwartz[7] proposed that since the dense fibrotic ridge across the superior margin of the right sinus of Valsalva was a common observation the turbulence produced by this ridge might lead to localized aneurysmal dilatation of the aorta with eventual rupture into the left ventricle Massive vitamin D or calcium ingestion during pregnancy also was considered as a possible cause of the faulty embryological devel opment In our case the tunnel resembled a large artery with three layers and atherosclerosis and was similar to that reported by Levy and colleagues[3] Our findings favor the hypothesis that the tunnel is an anomalous coronary artery although it contains purely elastic media without a cohesive muscular coat as one would expect to find in a coronary artery There is no evidence of medial cystic necrosis in our specimen Despite the fact that the tunnel is an artery the patho genesis remains unsettled because of insufficient ly convincing evidence to explain the embryolo gy

Of the 22 patients 17 had surgical correction The youngest to undergo operation was five months of age Three patients (18 per cent) died in the perioperative period two of which were believed to be related to uncorrected aortic steno sis[3 5] After operation 11 patients were improved although eight continued to have mild aortic insufficiency Three patients were asymptomatic both before and after surgery Among the five patients who were not operated upon three died early in childhood of congestive heart failure one died at age four following varicella infection and congestive heart failure and one died suddenly at age 14 without previous symptoms

Based on available data one can reasonably assume that surgery of this anomaly is the treat ment of choice especially in symptomatic patients However long term follow up data have not been reported The high incidence of asso ciated cardiac defects such as valvular aortic stenosis and incompetence may increase the surgical risk and alter the clinical course follow ing operation With the cooperation of previous authors[3 8 11 1 11] the follow up information of eight patients was available Six continued to do well with mild aortic insufficiency three to six years after operation Two patients had severe aortic insufficiency One underwent reoperation seven years after initial correction of the tunnel and died shortly following the second operation Another patient may require aortic valve replace ment in the near future Progressive valvular aortic incompetence in some of the surviving patients was impressive and suggests that the aortic valvular lesion is congenital and may even be a part of the malformation The consensus among the authors[1 4] is that the tunnel should be closed at an early age It is likely however that approximately 50 per cent of patients will require further surgical treatment of the aortic valve at a later time with the attendant additional surgical risk

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Low-dose heparin: Is the risk worth the benefit?

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Primary prevention of venous thromboembolism

Although the *reported* incidence of pulmonary embolism varies widely depending on the source, criteria, and accuracy of the data evaluated,[1] it has been conservatively *estimated* that venous thromboembolism causes in excess of 50,000 deaths annually in the United States.[2-4] Most of these deaths are hospital based and complicate traumatic, postoperative, and post partum states, acute myocardial infarction, congestive heart failure, acute pulmonary insufficiency, shock, estrogen therapy, gram negative sepsis, polycythemia vera, prolonged immobilization, certain dysproteinemias, and several malignant tumors. In patients with cancer, pulmonary embolism may in fact be the cause of death. There are, moreover, patients with genetic abnormalities such as homocystinuria and antithrombin III deficiency who are prone to develop thrombosis.

Despite its ubiquity, venous thromboembolism is an age-dependent phenomenon that is unexpectedly lethal, although surprisingly benign considering its high frequency. The therapeutic implication of this *statement* is that it becomes essential to treat the many to benefit the few.

Although heparin has been clearly demonstrated to prevent venous thrombosis and pulmonary embolism in man, the drug has not had a significant impact *on* the mortality rate from pulmonary embolism in the past quarter century.[5-7]

If this analysis is valid, the question must be asked: Why is not heparin *more* generally used as primary prophylaxis to prevent lethal pulmonary embolism or disabling venous insufficiency? Hesitancy to use heparin more widely stems *from* the risk of major drug induced bleeding which laboratory monitoring does *not* prevent; thus the compound has been either withheld until after the occurrence of a thromboembolic event or restricted to high risk patient populations. What is clearly needed is a heparin regimen in which the bleeding risk is slight enough to be acceptable to physicians, can be administered in a standard fashion without laboratory monitoring, and can therefore be used widely in patients prior to the thrombotic event. Unless such a goal can be achieved, heparin will never significantly reduce deaths from pulmonary embolism. Due to the ubiquity of venous thromboembolism compared to the relative infrequency with which it causes or contributes to death, however, individual physicians will never be aware of their successes but will always be reminded either of prophylactic failures, whether these are spontaneous, traumatic, or thrombocytopenia induced hemorrhage on the one hand, or of thromboembolism on the other. Therefore the conclusions from the data in clinical trials, many of which admittedly have defects,[8] need to gain general acceptance.

The regimen of low-dose heparin offers, for the first time, the possibility of using this drug as an agent of primary prophylaxis against lethal pulmonary embolism among a wide variety of patients at varying risk of venous thromboembolism.

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Molecular basis for the efficacy of low dose heparin

In retrospect hints concerning the possible prophylactic value of low dose heparin can be found among the early reports on the use of the drug to prevent thrombosis in animals and man.[8,14] It was not however until 1966 that the prophylactic use of small doses of heparin for the prevention of postoperative thrombosis was actually undertaken and reported by Sharnoff.[15] All of these publications anticipated the results of the controlled clinical trials of the 1970s.

The heparin story in fact spans an 80 year period. Before the turn of the century Contejean[16] suggested that an inhibitor to thrombosis existed in normal plasma. In 1939 Brinkhous et al[1] observed that the anticoagulant effect of heparin occurred only in the presence of a plasma component called heparin cofactor. Although originally disputed it is now accepted that antithrombin III is identical with heparin cofactor.[1]

Charles Best in 1948 suggested that the study of thrombosis might advance more rapidly if attention was focused on why blood remains fluid within the circulation rather than why it gels. Although an implication of this remark was that the plasma inhibitors might hold a key to anti thrombotic therapy the importance of this shift in emphasis from procoagulant to anticoagulant research had to wait more than a decade until investigations of the plasma inhibitors of the clotting proteases provided the insights to examine nature s defense mechanism against excessive intravascular coagulation.

In 1962 Seegers and Marciniak[9] found that an antithrombin III fraction isolated from bovine plasma could also neutralize X the activated species of clotting factor X and concluded that antithrombin III and anti X were one and the same plasma substance. Other developments also served as important building blocks to the conceptual development of a new use of heparin. In 1964 Davie and Ratnoff[19] in this country and MacFarlane in England independently developed the concept of the sequential activation of clotting factors that identified the pivotal role of factor X as the zymogen located at the beginning of the final biochemical pathway to fibrin formation. Three years later Barton and colleagues[2] demonstrated that X was the serine protease in the prothrombinase complex responsible for the activation of prothrombin to thrombin and Yin and Wessler found in animals that X was more thrombogenic than thrombin on a molar basis.

In 1971 it was noted[23] that trace amounts of heparin in human plasma had the capacity to increase markedly the X antithrombin III reaction rate. This observation led to the suggestion that one primary role of heparin in preventing thrombosis might be the potentiation of X inhibition by antithrombin III.[2] Based on the concept of biochemical amplification in blood coagulation[24] and the ability of antithrombin III to inhibit X rapidly in the presence of small quantities of heparin it was proposed that less heparin is required to inhibit thrombosis prior to thrombin formation than afterward.

It was with this background that a remarkably large number of controlled clinical trials of low dose heparin (facilitated by improvements in venography and limb and lung isotope scanning) were initiated in 1971 and continue to the present time first in surgical patients and then in other conditions associated with pulmonary embolism.

Although in vitro experiments showed that antithrombin III by itself only slowly inhibits serine proteases of the coagulation system except for X and thrombin Rosenberg[1] demonstrated that antithrombin III in the presence of heparin rapidly inhibits activated factors IX XI XII and plasmin. Thus heparin has a major function in facilitating the inhibition of thrombosis in the intrinsic clotting system as well as the final common pathway leading to fibrin gel formation.[27] In this role heparin acts as a catalyst[30] increasing the rate of the protease inhibitor reaction without being consumed and without altering the final products of the reaction.[26]

Clinical data

Surgery. In the four year period 1971 to 1975 more than 20 trials of low dose heparin in over 2 000 surgical patients monitored by I 125 fibrinogen limb scanning and/or venography demonstrated with one exception a significant decrease in deep vein thrombosis in the treated compared to the control groups.[31] Numerous confirmatory trials have been published subsequently. Because of the small number of patients in each of these studies however no conclusions could be reached concerning the prevention of postoperative pulmonary emboli.

To determine whether low dose heparin in surgical patients diminished postoperative

pulmonary emboli two large clinical trials were undertaken In one, 4 121 patients were involved[3] and in the other there were 500 patients[33] Although neither trial contained sufficient subjects to demonstrate a difference in mortality rate between treated and control groups the autopsy findings revealed significant differences in the incidence of large pulmonary emboli (those that could have caused or contributed to death) Among the 4,621 patients in the two trials the ratio of large pulmonary emboli in the control versus the treated group was 5 1 The p value was less than 0 0005 Thus despite the failure to demonstrate an over all mortality rate difference it can reasonably be inferred that the survival benefit attributable to the anticoagulant is real It is on this inferential argument that the value of low dose heparin in surgical patients is based and is supported by the substantial number of trials in various countries demonstrating a decrease in postoperative deep venous thrombosis—the source of 95 per cent of pulmonary emboli. On the negative side most trials have also documented that low dose heparin regimens cause a definite increase in minor wound hematoma and postoperative bleeding Although some surgeons find the hemorrhagic risk small enough to be acceptable others clearly do not[3, 35] and this key issue requires resolution

Examination of all available data support the value of a low dose heparin regimen in the prevention of postoperative venous thrombosis and pulmonary embolism in hemostatically competent patients over the age of 40 subjected to elective major abdominal and thoracic operations with the following provisos limitations, and exceptions All patients prior to therapy should receive a laboratory screen including an hematocrit prothrombin time partial thromboplastin time and platelet count It should be determined prior to operation that the patient is not on oral anticoagulants and did not receive platelet antiaggregating agents such as aspirin within five days before surgery since these drugs together with heparin can augment operative or postoperative bleeding Despite conflicting claims low-dose heparin regimens are presently believed to be of limited value or inadequate in open prostatectomy and major orthopedic procedures especially repair of femoral fractures and reconstructive operations on the hip and knee No data are available on prophylaxis for emergency surgery or trauma Low dose heparin prophylaxis is also considered inadequate for patients undergoing operation during an active thrombotic process Whether in selected patients to initiate low dose heparin on entry to the hospital or to continue anticoagulant therapy after discharge should be decided on an individual basis[35]

Most trials have used heparin doses ranging from 10 000 to 15 000 units per day subcutaneously in divided doses The most common regimen have been 5 000 units initiated two hours before operation and repeated every eight or 12 hours until the patient is ambulatory or discharged Available evidence suggests that 5 000 units twice daily is as effective as and is associated with less bleeding than 5 000 units administered every eight hours This issue is heightened by claim that the USP unit is approximately 10 per cent more potent than the international unit used by Canadian and European investigators It is for these reasons that in the United States the recommended dose for surgical patients restricted to 10 000 units per day When using the low-dose schedule there is no need to monitor the effect of heparin by laboratory tests[36]

Although this formulation may be helpful to surgeons it must be recognized that all possible complications of the recommended prophylaxis cannot be foreseen at the present time Accordingly there will be instances in which the individual physician will correctly decide in special situations or in patients over the age of 40 but at extremely low risk of venous thromboembolism not to employ low dose heparin prophylaxis Conversely in patients under the age of 40 who are at increased risk (e g previous phlebitis or pulmonary embolism cancer congestive heart failure or on estrogen therapy) the physician may wish to use the low-dose regimen

Acute myocardial infarction Populations of patients hospitalized with acute myocardial infarction have been examined for deep venous thrombosis by I 125 limb scanning and several studies have compared the incidence of isotopic thrombosis in control and low-dose heparin groups[3] The over all evaluation of this admittedly limited experience permits the following observations (1) deep venous thrombosis is as common in acute myocardial infarction as in the postoperative state (2) the presence of congestive heart failure increases the frequency of leg vein

thrombosis (3) low-dose heparin significantly reduces the incidence of positive limb scans (4) when low doses of heparin were used no bleeding was encountered except for small hematomas at drug injection sites or if intramuscular injections were inadvertently administered (5) no increases in arrhythmias nor instances of hemorrhagic cardiac tamponade were reported among heparin treated patients Because of the small size of the trials no data were available concerning the effect of low dose heparin on mural thrombi systemic emboli or pulmonary emboli

One of the questions occasionally posed regarding the use of heparin in patients with acute myocardial infarction is whether the drug will increase ventricular arrhythmias Even though the plasma free fatty acids become elevated there has been no evidence of an increase in ventricular ectopic beats or other ventricular arrhythmias at least in patients without shock or pulmonary edema [9] nor in patients with stable coronary artery disease have there been any detrimental alterations of myocardial metabolism or mechanical performance [5]

Finally in the large multinational surgical trial referred to earlier [3] 13 patients in the control group and seven in the heparin group died of postoperative acute myocardial infarction Although these differences are not statistically significant they support previously reported observations of Sharnoff and DeBlasio [1] that the prophylactic administration of low dose heparin may also reduce postoperative fatalities from myocardial infarction and raise the question as to whether heparin as opposed to coumarin compounds can diminish the incidence of acute myocardial infarction

In hemostatically competent patients with heart attacks there appears no reason why 5 000 USP units subcutaneously cannot be used three times rather than twice daily as recommended for surgical patients

Stroke That deep vein thrombosis can develop in patients with paralytic strokes was documented in the early part of the nineteenth century [5, 53] More recent studies using I 125 limb scanning have demonstrated an average incidence in excess of 50 per cent mostly but not exclusively in the paralyzed extremity [54, 6] In one of these reports the incidence of pulmonary embolism was approximately 10 per cent [5] In another low-dose heparin was used in non hemorrhagic strokes and was found to reduce significantly the incidence of istopic limb thrombi [56] Moreover a recent report suggests the safety of low-dose heparin in elective neurosurgical procedures [57] Taken together these limited observations raise but do not resolve the question as to whether patients with non hemorrhagic strokes should be treated prophylactically with a low dose heparin regimen Further studies are clearly warranted

Respiratory failure There is little information on the value of low dose heparin among patients with respiratory failure—a group in whom pulmonary embolism is not uncommon One investigation has been reported which although it was not a controlled trial strongly suggested that the antithrombotic regimen significantly reduced the incidence of pulmonary emboli in a respiratory intensive care unit without drug induced hemorrhage [5]

Estrogen therapy That patients receiving estrogen therapy have an increased tendency to venous thromboembolism acute myocardial infarction and stroke is well established The data come from the use of estrogens to prevent conception [59-63] lactation [6] the progression of coronary heart disease [65] and the spread of certain malignancies [66, 67] Further men experiencing heart attacks at young ages have higher than normal circulating levels of endogenous estrogen [65] Finally as a risk factor for thrombosis the estrogen effect is dose dependent [9] and has an additive effect when combined with surgery [71, 7] or cigarette smoking [73]

Many elements of the clotting process have been described as abnormal among patients receiving estrogen containing oral contraceptives [7] It has been suggested that the effect of estrogen is not to decrease the quantity of antithrombin III but rather to retard the reaction rate between antithrombin III and X (X inhibitory activity)—an effect that in vitro can be immediately reversed by small doses of heparin [5] Proof of an intimate relationship in vivo between a decrease in X inhibitory activity and thrombosis as well as the prevention of intravascular coagulation by small doses of heparin has been strongly suggested in patients [76] and confirmed in animals [4] In this latter study it was clearly demonstrated that while estrogens were not themselves thrombogenic they aggravated in a dose related manner the severity of the thrombogenic stimulus and that the estrogen effect on

thrombosis could be completely eliminated by small doses of heparin

These studies indicate a role for low dose heparin regimens in a variety of clinical conditions in which estrogen therapy is employed

Immobilization The immobilized state while not itself initiating intravascular coagulation [77] is associated with a real but variable incidence of venous thromboembolism depending in part on patient age the degree and duration of immobilization and the nature of the underlying process These processes include injury orthopedic neurologic infectious cardiac pulmonic and malignant conditions Some of these patients die prematurely of pulmonary embolism Whether selected portions of this large population will benefit from prophylactic low dose heparin regimens during their periods of immobilization is yet to be determined and certainly warrants investigation

Comment

The use of low dose heparin in clinical trials was initially attempted among elective surgical patients by Kakkar and colleagues using isotope limb scanning because such patients as a group are not actively clotting prior to operation and the molecular basis for the efficacy of the regimen requires that prophylaxis be instituted prior to the onset of intravascular coagulation [7] Since many thrombi form during or immediately after operative procedures it was deemed appropriate to begin therapy shortly *prior to operation*—a view held earlier by Sharnoff and associates [8] The dozens of surgical trials completed in the 1970s when taken together have demonstrated with the exception of certain operative procedures [6] a significant decrease in postoperative venous thromboembolism

Recognition of the effectiveness of the therapy does not assume its widespread use in clinical practice unless the risk-benefit ratio is acceptable Many effective therapies have fallen by the wayside because the hazard outweighed the value Guidelines to minimize risk in surgical patients have been published [18] Nevertheless the problem of drug induced hemorrhage even if thought by some to be minor must be acknowledged In the published trials no effort was made to eliminate aspirin or other antiaggregant compounds preceding the operative procedure Aspirin itself can cause bleeding in surgical patients and the combination of aspirin and low doses of heparin induces a double hemostatic defect with a likelihood of hemorrhage greater than with either drug alone Aspirin may in fact account for some of the bleeding observed among control patients in many of the trials Thus if the caveat is honored that patients given low dose heparin should not receive aspirin for five days prior to operation it can be anticipated that there will be even less bleeding from low dose heparin than has been recorded in past trials Finally monitoring the platelet count can alert the physician to the rare possibility of thrombocytopenia that may be induced by heparin in the postoperative period But above and beyond those precautions it should be recognized that to prevent thrombosis even with small quantities of heparin the hemostatic mechanism is sufficiently unbalanced that the risk of bleeding can be aggravated by invasive vascular procedures intramuscular injections and the not infrequent reported and unreported injuries that hospitalized patients sustain

The value of low dose heparin addresses itself to primary prophylaxis from thromboembolism involving millions of patients not just with surgically approachable lesions but with myocardial infarction congestive failure arrhythmias stroke pulmonary insufficiency conditions utilizing estrogen therapy and illnesses requiring periods of prolonged immobilization In most of these conditions the risk of hemorrhage is less than in major surgery however definitive trials of efficacy have not been performed and the use of a low dose regimen can only be advanced by analogy with the efficacy presently observed in the surgical population

Even if prophylaxis is accepted on the basis that benefit outweighs risk there still remain two hurdles that must be overcome First because of the great discrepancy between the ubiquity of venous thromboembolism and the relative infrequency with which it causes death the individual physician no matter how extensive his personal practice will never recognize the success of his prophylactic action yet will invariably be reminded of his failures The second hurdle is one of the *visibility* of benefit in the total population and can be illustrated by contrasting two pathologic processes with numerically comparable sequelae of differing visibility Poliomyelitis vaccination protects 10 000 individuals per year

from disabling neurologic defects and nationally this benefit is readily apparent to physicians and laymen alike But an achievable diminution in lethal thromboembolism and hemiplegia from low dose heparin in just two conditions general surgery and acute myocardial infarction comparable in numbers to the 10 000 polio cases will not be as clearly appreciated for it will be submerged in autopsy statistics that may never see the light of day[81] If one extends this analysis to the thousands of patients at risk of thromboembolism from other disease states mentioned earlier then the potential impact of low dose heparin on survival and the quality of life exceeds in numbers the success achieved by poliomyelitis prophylaxis It is doubtful that this handicap of visibility can be overcome and if it is not low dose heparin may never exert a favorable impact on the more than 50 000 patients who die annually of pulmonary embolism most of them in hospitals rehabilitation centers or nursing homes

It would be inappropriate to press the case for low dose heparin beyond the available data Presently unforeseen modifications of the heparin molecule may diminish some of its adverse effects or its need for parenteral administration and other therapies may prove themselves superior For the present acceptance will depend as it should on the physician s answer to the question in each patient is the risk worth the benefit?

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The prevention and treatment of bacterial endocarditis

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Infective endocarditis may be caused by bacteria fungi rickettsia (Q fever) and possibly *Chlamydiae* and viruses[1] multiplying on endocardial surfaces In addition trichinosis has been reported to cause extensive ventricular mural endocarditis with superimposed thrombosis[2] This review will consider only the bacterial form of the disease Usually it is the endocardium of the heart valve that is involved by bacteria with infection of a cardiac prosthesis involving tissues surrounding the prosthesis or sutures Rarely the suture or prosthesis alone is involved

The gross appearance of bacterial endocarditis usually results in lesions called vegetations Microscopically the vegetation is composed of masses of fibrin platelets and microorganisms with little cellular reaction Research by Durack and Beeson[3] indicates that the microorganisms are embedded within the fibrin-platelet meshwork and are therefore protected from the defense mechanisms of the host Enhancing this problem is the reduced state of metabolic activity of the bacteria deep within the lesion thus reducing the effectiveness of most antimicrobial agents directed against them The polymyxins and amphotericin B are unique in that they act on contact with susceptible organisms regardless of metabolic activity Unfortunately they have limited usefulness in the treatment of bacterial endocarditis

Another factor that creates difficulty in therapy is depression of bactericidal activities of the polymorphonuclear leukocytes from untreated patients with bacterial endocarditis The observation of a rapid return to normal bactericidal function during treatment indicates that the depression is an acquired consequence of the infectious process of bacterial endocarditis Thus this type of infection tends to perpetuate itself by depressing normal host defense mechanisms This depression may well explain the constancy of bacteremia until antibiotic therapy in most patients[4]

The question of whether the lesion always occurs on previously damaged valves or sometimes on undamaged valves is controversial The possibility that bacteria may invade a normal valve by passing through the vessels supplying that valve has been suggested,[5-9] but normal appearing valves usually have little or no vascularization and bacterial endocarditis does occur on such valves Another suggestion is that bacteria may settle on sterile thrombotic areas on valve surfaces[1-13] This appears to be a more likely mechanism in those patients without previous valvular disease and has been shown to occur in an experimental rabbit model[14] However, bacteria flowing past thrombotic areas in other parts of the body apparently do so without adherence and production of disease most of the time so there must be something about the endocardium that is unique

Another mechanism of adherence to the endocardium is reported by Gould and colleagues[15] certain gram positive pathogenic bacteria such as enterococci *Staphylococcus aureus Staphylococcus epidermidis* and alpha hemolytic streptococci have surface components that react with receptors on the endocardial cell surface This finding correlates with the clinical observation

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that gram positive bacteria cause endocarditis more frequently than gram negative bacteria However adherence due to receptors is not the only determinant of the virulence of bacteria since some bacteria such as Group A beta hemolytic streptococci have good adherence properties but are not frequently associated with endocarditis To complicate matters further *Cardiobacterium hominis* a slow growing gram negative bacillus has rarely produced a recognizable disease in man other than endocarditis The mechanism of this organ tropism is unknown[1] Improvement in the prevention and therapy of bacterial endocarditis will come with better understanding of the pathophysiology of the lesion and the bacteria that produce it

Diagnosis

In modern times the diagnosis of bacterial endocarditis is difficult if one relies on descriptions of the disease prior to 1960[7,18] Because today s patients rarely allow symptoms to go untreated for a long time the physician is usually confronted with vague symptoms that may easily be assigned to a more benign disease Fever and heart murmur are enough to raise one s suspicion of bacterial endocarditis but demonstration of the causative microorganism at the site of the pathological lesion is the only definite means of diagnosing the disease Because such demonstration is not possible except from surgical or pathological specimens blood cultures that demonstrate the continuous presence of one or more microorganisms lead to a presumptive but usually accurate diagnosis of bacterial endocarditis As emphasized recently by Miller and Casey[9] the recognition of predisposing factors such as congenital or valvular heart disease recent heart surgery with or without insertion of a cardiac prosthesis or narcotic addiction can lead to the proper diagnosis in spite of the absence of the classical Osler s nodes splenomegaly Roth s spots etc In the final analysis the clinical presentation is determined by the virulence and type of the infecting bacterium which influences the degree of dysfunction due to valve injury complications of peripheral embolization and vasculitic reactions presumably resulting from hypersensitivity

When the diagnosis of bacterial endocarditis is suspected continuous bacteremia is usually rather easily confirmed The patient with a heart murmur and fever needs no more than five blood cultures drawn over a 48 hour (or less) period Each sample is cultured both aerobically and anaerobically and the laboratory is requested to hold the cultures for at least two weeks and preferably three weeks If a fastidious organism such as *Brucella abortus* is suspected the laboratory should be informed Drawing several blood samples improves the chance of identifying the actual causative bacterium which will usually appear in all of the cultures whereas a contaminant might appear in only one[11] Rarely more than one bacterium appear in successive cultures When this occurs both bacteria should be considered causative and antibiotic therapy should be adequate for all bacteria repeatedly cultured However the likelihood of more than one bacterium being an etiological agent is small even in the case of immunologically suppressed patients

Continuous bacteremia associated with a heart murmur means bacterial endocarditis until proven otherwise In the geriatric patient especially fever may be absent and the initial manifestation may be the result of embolization such as a cerebrovascular accident or organic psychosis but bacteremia can be demonstrated On the other hand a patient may have a heart murmur and continuous bacteremia with Brucella or Salmonella and *not* have endocarditis Secondly some patients with intermittent bacteremia caused by gram negative bacilli from an intra abdominal abscess or other source frequently have murmurs and do not have endocarditis at autopsy Nevertheless in both of these situations endocarditis is *also* possible and the burden of proof rests on the physician who says that the disease does not exist

Diagnostic measures other than blood cultures usually cannot prove endocarditis but they can suggest it Teicho c acid antibody tests have been found to be a rapid method of diagnosing *Staphylococcus aureus* endocarditis Nagel and associates compared the agar diffusion and counterimmunoelectrophoresis (CIE) methods for detecting teichoic acid antibodies and their study showed the agar diffusion technique to be less sensitive than the CIE (85 per cent vs 96 per cent respectively) with a longer preparation time (plates read in 18 to 72 hours vs 1 hour respectively) but the agar diffusion technique did have a greater specificity (less than 5 per cent false

positive vs 10 per cent false positive respectively) It has been recommended that both tests be used the CIE for screening and the agar diffusion for confirmation The teichoic acid antibody levels usually are high enough to be detected by the time of admission to the hospital and are useful in following therapy because they will fall and disappear with successful treatment When the diagnosis is not sufficiently clear or previous antimicrobial therapy has rendered the blood cultures negative, this test can give the clinician an early presumptive diagnosis to base therapy upon until the standard cultures are reported Because the teichoic acid antibody test may be positive with other deep seated *Staphylococcus aureus* infections such as osteomyelitis a thorough knowledge of the patient s condition is mandatory before proper interpretation can be made In addition some false positive results have been obtained when the infecting organism was *Staphylococcus epidermidis* but these probably are due to antibodies against the ribitol-teichoic acid Recently an solid phase radioimmunoassay for the detection of *Staphylococcus aureus antigen* has been evaluated in rabbits with endocarditis A similar method has been useful in diagnosing cryptococcal meningoencephalitis in patients with negative cultures

Other diagnostic measures that are occasionally helpful include examination of gram stains of buffy coat preparations of peripheral blood testing for elevated erythrocyte sedimentation rates rheumatoid factor and looking for circulating immune complexes [5] The erythrocyte sedimentation rate is a very sensitive test being elevated in close to 100 per cent of cases [18, 26, 2] but unfortunately it is nonspecific The test for rheumatoid factor is also not specific but it correlates well with endocarditis lasting six weeks or longer [8] and the titers for this test usually fall and disappear with adequate treatment The function of the IgM rheumatoid factor in bacterial endocarditis is not understood It appears to enhance bacterial agglutination *in vitro* but inhibits opsonization of microorganisms when tested with autologous serum More likely it simply represents IgM response to the Fc fragment of the IgG involved in the initial coating of the offending bacterium for the classical complement pathway for opsonization and phagocytosis Circulating immune complexes especially in high titers may be useful in diagnosis and are also believed to result in vasculitic lesions in the skin and kidney A fall in serum complement is an early finding in these patients

Although the role of echocardiography in diagnosis of endocarditis is less than its potential usefulness in predicting which patient will require operation (those with large vegetations and/or premature closure of an infected mitral valve especially with aortic incompetence for example), echocardiography and gallium-67 imaging may be helpful diagnostically in the 15 per cent to 20 per cent of patients with bacterial endocarditis and negative blood cultures

A growing concern is the reported association of *Streptococcus bovis* endocarditis and colonic cancer prompting several authors[30, 3] to suggest a causal relationship between the two Two hypotheses for the relationship have been suggested (1) that carcinogens are elaborated by the infecting *Streptococcus bovis* organisms and (2) that colon cancer induces an environment that allows an overgrowth of *Streptococcus bovis* thus inducing a carrier state In the carrier state because of decreased local host defense mechanisms as the result of the tumor, bacteremia leading to infection of the endocardium may result I favor the latter concept In either case Klein and colleagues[31] recommend differentiating group D streptococci by species so that patients with *Streptococcus bovis* endocarditis can be investigated for gastrointestinal lesions and in particular colonic carcinoma

Prosthetic valve endocarditis

Involvement of the prosthetic valve, sutures, and especially the surrounding endocardium with bacteria is a special problem that has resulted from modern medical advances [31] These types of endocarditis are usually divided into early onset (those cases occurring two months or less postoperatively) and late onset (those cases occurring longer than two months postoperatively) [34] The organisms usually isolated from prosthetic valve endocarditis include *Staphylococcus aureus* *Staphylococcus epidermidis* alpha and beta hemolytic streptococci diphtheroids, gram negative bacilli and fungi such as *Candida* and *Aspergillus* species A substantial number of the early-onset cases are caused by gram negative bacilli probably due to hospital acquired infections As a matter of fact, endocarditis due to gram negative bacteria is infrequent except in this setting and in drug addicts

The question then arises as to how to differentiate gram negative bacteremia from gram negative endocarditis in patients with prosthetic valves According to Sande and co workers[10] if no definitive signs of endocarditis appear such as a new or changing murmur petechiae or other signs of embolic phenomena then the patient should be examined for extracardiac sources of infection such as pneumonia wound sites intra vascular or urethral catheters phlebitis or cellulitis If the same organism that is causing the bacteremia can be isolated from any of these sites then it is more likely that this is the source and the patient does not have prosthetic valve endocarditis Obviously this can be a difficult clinical decision and one that may be helped by the use of echocardiography

All possible sites of bacteremia should be removed or treated since when a bacteremia is present a potential for prosthetic valve endocarditis is always there Another complicating factor is that patients with early prosthetic valve endocarditis have almost invariably received prophylactic antibiotic(s) before operation Therefore the bacteria causing the endocarditis have most likely become resistant to the antibiotic(s) used for prophylaxis Different antibiotics with bactericidal activity against the specific gram negative bacillus are thus indicated If no endocarditis is established a short course of antibiotic therapy (7 to 10 days) should be sufficient to eradicate bacteremia providing the source such as an intravascular catheter is removed

Bogart and colleagues[41] have taken an opposing view They concur about the high incidence of gram negative bacteremia in prosthetic valve patients but point out that the criteria used by Sande and associates[10] may be too general In Bogart and colleagues study 20 per cent of cases of early prosthetic valve endocarditis were caused by gram negative organisms but in only about 50 per cent of these did a new or changing murmur develop Thus an extracardiac source of bacteremia should not militate against the chance of endocarditis and in fact may be the source of the endocarditis They[41] conclude that any prosthetic valve patient with a gram negative bacteremia should be treated as though he has endocarditis

Watanakunakorn[2] has pointed out that medical progress in areas other than the installation of prosthetic valves has played a role in producing bacterial endocarditis He is particularly concerned with the increasing incidence of *Staphylococcus aureus* endocarditis associated with intravenous lines shunt infections in patients undergoing long term hemodialysis and in infections associated with permanent intracardiac pacemakers Even intrauterine devices have been incriminated as a cause of bacteremia and endocarditis

Prophylaxis

Much emphasis is placed on the prophylaxis of bacterial endocarditis when bacteremia appears imminent in a patient with congenital or valvular heart disease However prevention of the heart disease itself would be a more desirable prophylaxis Rheumatic fever is believed to account for most of the cardiac disease underlying endocarditis[43] and its prevention would certainly lower the incidence of endocarditis All group A beta hemolytic streptococcal infections should be treated with suitable antibiotics Prophylactic penicillin or sulfadiazine is helpful in preventing exacerbations of rheumatic fever[44] in patients who did not have severe endocarditis with the original attack.

Congenital heart disease is said to account for 6 to 24 per cent of predisposing cardiac problems, and perhaps even more if mitral valve prolapse is considered congenital Ventricular septal defect and patent ductus arteriosus are the congenital defects thought to have the highest risk of predisposing to endocarditis[5] but it is estimated that at least 5 per cent of all women have a prolapsed mitral valve with a murmur and/or systolic click and more cases of endocarditis probably come from this group

Infection with rubella during the first trimester of pregnancy has been associated in the fetus with patent ductus arteriosus (58 per cent of cases) ventricular septal defect tetralogy of Fallot atrial septal defect and pulmonary stenosis all of which are associated with endocarditis[46] Thus administration of rubella vaccine to all children should decrease if not eliminate this problem Other viruses such as Coxsackie B are also associated with congenital heart defects when infection occurs during pregnancy especially in the third trimester No vaccine is presently available for this group of viruses

Any patient with a heart murmur should receive pneumococcal vaccine at appropriate

intervals and influenza vaccine annually Theoretically if these diseases are avoided, there will be less opportunity for bacteremia from the upper respiratory tract Both of these vaccines are well tolerated influenza vaccine being absolutely contraindicated only to persons who are allergic to eggs

A frequently overlooked form of prevention of endocarditis is proper education of patients who are at risk. Persons with heart murmurs should be told to watch for symptoms of illness which may indicate bacteremia and to seek prompt treatment Minor injuries sore throats and furuncles may seem innocuous to patients but it has been shown that compressing a boil use of a Water Pik dental manipulations and even chewing mint candy can result in transient bacteremia [7] Obviously it is impossible to maintain continuous prophylaxis nevertheless if the degree of bacteremia is likely to be great in instances such as incision and drainage of an abscess or removal of an infected tooth, antibiotic therapy should be initiated.

Antibiotic prophylaxis for patients at high risk of endocarditis remains controversial The toxicity of the antibiotic(s) has to be weighed against the risk It has been recommended that patients suspected of having nonbacterial thrombotic endocarditis (NBTE) and those suspected of having idiopathic hypertrophic subaortic stenosis[8,9] receive antibiotic prophylaxis when facing potential bacteremia however not all authors agree on antibiotic prophylaxis for patients with mitral valve prolapse (MVP) Jeresaty[10] and others [1] stipulate that antibiotic prophylaxis is indicated for MVP patients only when a murmur of mitral insufficiency is heard On the other hand Aranda and colleagues reported that antibiotic prophylaxis is justified in all patients with MVP and De Silva and co workers reported that they advised an MVP patient to take antibiotics before any procedures likely to cause bacteremia My present policy is to recommend antibiotic prophylaxis for all patients with a murmur and also for all patients with a systolic click that is confirmed to be mitral valve prolapse by echocardiography

In 1965 the American Heart Association published a 3 page brochure on the prevention of bacterial endocarditis The purposes for using antibiotics were simply stated to (1) prevent bacteremia or reduce its magnitude and duration should it occur and (2) eradicate bacteria that may implant on heart valves before a vegetation is formed In July of 1977 another American Heart Association Committee on the prevention of bacterial endocarditis published their recommendations [5] The committees were made up of different physicians even though many of the members of the 1965 committee are still active The 1977 recommendations state 'Since there have been no controlled clinical trials adequate data for comparing various methods for prevention of endocarditis in man are not available However an experimental animal model permitting consistent induction of bacterial endocarditis with microorganisms which often cause the infection in man has allowed experimental evaluation of both prophylaxis and treatment Data from these studies although derived from animal rather than clinical investigations represent the only direct information on the efficacy of prophylaxis that is presently available For medicolegal purposes the final warning paragraph of the committee s report is very important

Warning

The committee recognizes that it is not possible to make recommendations for all possible clinical situations Practitioners should exercise their clinical judgment in determining the duration and choice of antibiotic(s) when special circumstances apply Furthermore since endocarditis may occur despite antibiotic prophylaxis physicians and dentists should maintain a high index of suspicion in the interpretation of any unusual clinical events following the above procedures Early diagnosis is important to reduce complications sequelae and mortality

My policy is to follow the recommendations of the 1977 American Heart Association Committee report (Table I) but I agree with Petersdorf that 24 hours is long enough for the antibiotic(s) to be given because bacteremia secondary to procedures rarely lasts longer than 15 minutes. Initial doses of penicillin should be administered in the physician s or dentist s office in order that, in the rare instance of anaphylactic reaction appropriate treatment with epinephrine can be immediately instituted Hunt and co workers recently reported that erythromycin resistance is present in many oral alpha hemolytic streptococci suggesting that erythromycin as an alternative to penicillin is not justified I have given vanco-

For compl te details, see the statement Prevention of Bacterial Endocarditis, published in Circulation 56 139A 1977 Reprinted with permission of American Heart Association.

Table I Prophylaxis against bacterial endocarditis*

A *For dental and upper respiratory tract procedures*†

1 Penicillin therapy alone

a Parenteral-oral administration

(1) Adults Aqueous crystalline penicillin G (1 million units IM) mixed with procaine penicillin G (600 000 units IM) Give 30 min. to 1 hr prior to procedure Then give penicillin V (500 mg PO) every 6 hr for 8 doses.

(2) Children‡ Aqueous crystalline penicillin G (30 000 units/Kg IM) mixed with procaine penicillin G (600 000 units IM) Give 30 min to 1 hr prior to procedure For children weighing less than 60 lbs the dose of penicillin V is 250 mg PO every 6 hr for 8 doses

b Oral administration

(1) Adults Penicillin V (2 g PO) 30 min to 1 hr prior to procedure then 500 mg every 6 hr for 8 doses.

(2) Children‡ Same For children weighing less than 60 lbs use ½ the dosage for the same time schedule

2 Patients allergic to penicillin

a Adults Vancomycin (1 g IV over 30 min to 1 hr) Start infusion 30 min. to 1 hr prior to procedure Then give erythromycin (500 mg PO every 6 hr for 8 doses)

b Children‡ Vancomycin (20 mg/Kg IV over 30 min.–1 hr) Start infusion 30 min. to 1 hr prior to procedure Then give erythromycin (10 mg/Kg PO every 6 hr for 8 doses)

or use

c Adults Erythromycin (1 gm PO 1½–2 hr prior to procedure) Then give 500 mg. PO every 6 hr for 8 doses

d Children‡ Erythromycin (20 mg/Kg PO 1.5–2 hr prior to procedure) Then give 10 mg/Kg every 6 hr for 8 doses.

3 Penicillin plus streptomycin

a Adults Aqueous crystalline penicillin G (1 million units IM) mixed with procaine penicillin G (600 000 units IM) Plus, streptomycin (1 g IM) Give 30 min to 1 hr prior to procedure followed by penicillin V (500 mg PO every 6 hr for 8 doses)

b Children‡ Aqueous crystalline penicillin G (30 000 units/Kg/IM) mixed with procaine penicillin G (600 000 units IM) Plus, streptomycin (20 mg/Kg IM) For children weighing less than 60 lbs., penicillin V (250 mg. PO every 6 hr for 8 doses)

B *For gastrointestinal and genitourinary tract procedures*

1 Penicillin

a. Adults Aqueous crystalline penicillin G (2 million units IM or IV) or ampicillin (1 g IM or IV) Then give gentamicin (1 5 mg/Kg—do not exceed 80 mg IM or IV) or streptomycin (1 g IM) Give initial doses 30 min to 1 hr prior to procedure If gentamicin is used, give similar dose of it and penicillin (or ampicillin) every 8 hours for 2 additional doses If streptomycin is used, give a similar dose of it and penicillin (or ampicillin) every 12 hours for 2 additional doses

b Children‡ Aqueous crystalline penicillin G (30 000 units/Kg IM or IV) or ampicillin (50 mg/Kg IM or IV) Then give gentamicin (2 0 mg/Kg IM or IV) *or* streptomycin, (20 mg/Kg IM) Timing of doses is the same as for adults.

2 For patients allergic to penicillin

a Adults Vancomycin (1 g IV given over 30 min–1 hr) plus streptomycin (1 gm IM) Give 1 dose 30 min to 1 hr prior to procedure and if thought necessary repeat in 12 hours.

b Children‡ Vancomycin (20 mg/Kg IV given over 30 min. to 1 hr) plus streptomycin (20 mg/Kg IM) Timing of child s dose is the same as for adults. Total dosage should not exceed 44 mg/Kg/24 hours In case of prolonged procedures or delays in healing additional dosage may be necessary

3 For patients with prosthetic valves

a Adults Aqueous crystalline penicillin G (1 000 000 units IM)

mixed with

Procaine penicillin G (600 000 units IM)

plus

Streptomycin (1 gm IM)

Give 30 min to 1 hr prior to procedure then penicillin V (500 mg PO every 6 hrs. for 8 doses)

b Children‡ Aqueous crystalline penicillin G (30 000 units/Kg intramuscularly)

mixed with

Procaine penicillin G (600 000 units intramuscularly)

plus

Streptomycin (20 mg/Kg intramuscularly)

Timing of doses for children is the same as for adults For children less than 60 lbs the recommended oral dose of penicillin V is 250 mg every 6 hours for 8 doses

*Recommendations of a Committee of the American H art Association 1977 Reproduced with permission.

†In unusual circumstances or in the case of d layed healing addit on l doses of ntibiotics may be needed even though available data suggest that ba ter mia rarely persists lo ger than 15 minutes after the procedure The physician or d ntist may also choose to use the parenteral route of administrat n f r all of the doses in selected situation

‡Doses for children should not exceed recomm ndations fo adults for a single dose or for a 4 hour period.

intervals and influenza vaccine annually Theoretically if these diseases are avoided there will be less opportunity for bacteremia from the upper respiratory tract Both of these vaccines are well tolerated, influenza vaccine being absolutely contraindicated only to persons who are allergic to eggs

A frequently overlooked form of prevention of endocarditis is proper education of patients who are at risk Persons with heart murmurs should be told to watch for symptoms of illness which may indicate bacteremia and to seek prompt treatment Minor injuries sore throats, and furuncles may seem innocuous to patients but it has been shown that compressing a boil use of a Water Pik dental manipulations and even chewing mint candy can result in transient bacteremia[47] Obviously it is impossible to maintain continuous prophylaxis nevertheless if the degree of bacteremia is likely to be great in instances such as incision and drainage of an abscess or removal of an infected tooth antibiotic therapy should be initiated

Antibiotic prophylaxis for patients at high risk of endocarditis remains controversial The toxicity of the antibiotic(s) has to be weighed against the risk It has been recommended that patients suspected of having nonbacterial thrombotic endocarditis[8] (NBTE) and those suspected of having idiopathic hypertrophic subaortic stenosis receive antibiotic prophylaxis when facing potential bacteremia however not all authors agree on antibiotic prophylaxis for patients with mitral valve prolapse (MVP) Jeresaty and others[5, 53] stipulate that antibiotic prophylaxis is indicated for MVP patients only when a murmur of mitral insufficiency is heard On the other hand Aranda and colleagues[54] reported that antibiotic prophylaxis is justified in all patients with MVP and De Silva and co workers reported that they advised an MVP patient to take antibiotics before any procedures likely to cause bacteremia My present policy is to recommend antibiotic prophylaxis for all patients with a murmur and also for all patients with a systolic click that is confirmed to be mitral valve prolapse by echocardiography

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following the patient s progress If surgical intervention is elected for patients with severe congestive heart failure secondary to valve incompetance it should be done early Especially in prosthetic valve endocarditis in which mortality rates approach 60 per cent early surgical intervention has reduced the mortality rate to 41 per cent in one study [72] The indications for operation also include infections that are refractory to antibiotics or in the case of prosthetic valve endocarditis the presence of significant perivalvular leak in addition to the other criteria [3] Parrott and associates[73] reviewed the surgical management of bacterial endocarditis and pointed out that the mortality rate for infective endocarditis with congestive heart failure is high even with antibiotic therapy (79 to 89 per cent) whereas more aggressive surgical intervention can improve the prognosis In some instances patients can be cured by removal of an abscess or focus of infection outside the cardiovascular system [7, 74]

Modern principles of antibiotic treatment

Agents that are bactericidal as opposed to those that are bacteriostatic should be used because the rate of relapse is higher with the latter However even with *in vitro* bactericidal action the bacteria *in vivo* may simply become quiescent until the drug is stopped and then become active again [5]

Parenteral administration of antibiotic(s) is preferred over oral administration to minimize individual variation in absorption and compliance and to insure a dose that will be sufficiently high to produce a serum bactericidal level after the serum is diluted eight times However adequate studies have not been done to prove that 1 8 or greater dilution of serum is an optimal bactericidal level

Antibiotic therapy should be of sufficient duration to avoid relapse and produce cure Generally at least four weeks of therapy is necessary but 6 weeks or longer have been recommended for certain bacteria such as *Staphylococcus aureus* and enterococci

Antibiotic *in vitro* susceptibility of the bacteria involved should be determined using a broth dilution minimum inhibitory concentration *and* minimum bactericidal concentration The inhibitory concentration may be considerably lower than the bactericidal concentration and it is the latter that is important especially when using a drug such as vancomycin Obviously it would be advantageous to be able to correlate these concentrations with the level of antibiotic in the plasma or serum but practically most laboratories cannot do so with the exception of the radioimmunoassay for gentamicin tobramycin and amikacin

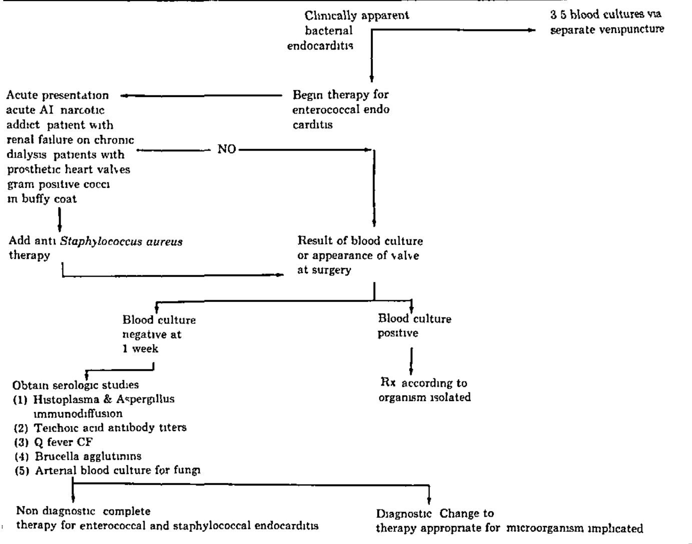
In the initial phases of antibiotic therapy for endocarditis bed rest is important as it is for any serious infection However there is always the risk of pulmonary embolism and thus again raises the question of the role if any of mini dose heparin The relationship of bacterial endocarditis and anticoagulation obviously needs further careful evaluation but the spectre of possible dangers remains

The antibiotic(s) should be able to penetrate fibrin to reach the bacteria deep within the vegetation The success of the penicillins is perhaps due in part to their ability to penetrate fibrin better than most other antibiotics

Initial antibiotic therapy before positive identification of the bacterium should be directed against those bacteria most likely to be causing the infection in the particular patient under consideration Alpha hemolytic streptococcal endocarditis remains the most frequent type Because it is rarely fulminant initial antibiotic therapy in the past was thought to be safely delayed until blood cultures were reported in 24 to 48 hours However we prefer to begin treatment as soon as five blood cultures are obtained in the patient with a strong suspicion of bacterial endocarditis If the patient has a prosthetic valve or is a drug addict therapy should definitely be started after no less than three blood samples are obtained and cultured for strict aerobes (*Pseudomonas aeruginosa* micrococci) and anaerobes (most bacteria) *Staphylococcus aureus* gram negative bacilli, or yeast is more likely in these situations

Obviously of importance in therapy is the consideration of whether or not the patient is hypersensitive to the proposed antibiotic This question most frequently arises if the patient is allergic to penicillin thinks he is allergic to penicillin or gives a history of rash following penicillin therapy especially with oral ampicillin Most of these patients do not have the type of hypersensitivity associated with immediate (Type 1) IgE mediated reactions However they must be assumed to have such types until proven

Table II Antibiotic treatment



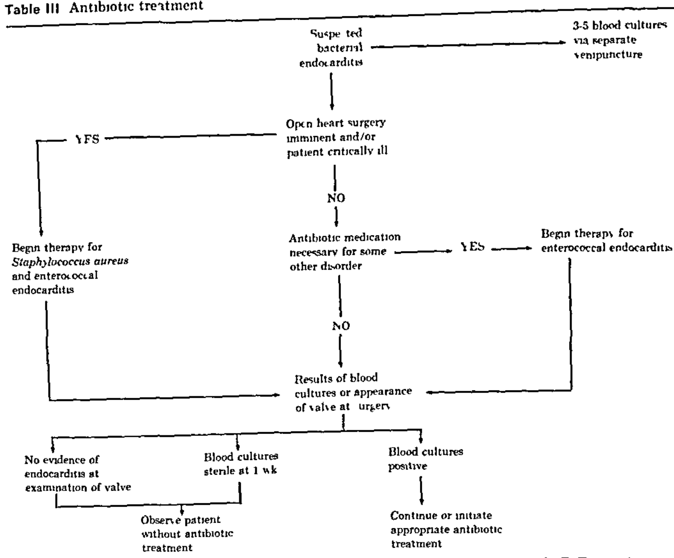
AI = aortic insufficiency

otherwise because a hypotensive episode is obviously an increased risk for a patient already ill with bacterial endocarditis A penicillin desensitization procedure is available if no alternative antibiotics are thought to be adequate Several protocols are available[76] Generally they start with low doses of penicillin G and gradually increase until massive doses can be given Penicillin hypersensitivity reactions that develop during therapy are not of the anaphylactic type and usually can be suppressed with other medications such as adrenal corticosteroids The penicillin therapy should not be interrupted because the risk of endocarditis is greater than the risk of any permanent damage from the penicillin reaction

Algorithms of treatment In 1976 the Infectious Diseases Society of America appointed a committee chaired by Pierce Gardner, M D to investigate the feasibility of developing guidelines for antimicrobial therapy Seven infectious disorders including infectious endocarditis were chosen as subjects for the initial effort C Glenn Cobbs M D Director of Infectious Diseases at the University of Alabama in Birmingham drafted the guidelines for infectious endocarditis and requested several of us to review the document[77]

As a part of the guidelines (which were never published) algorithms for treatment were designed and are included here with some modifications (Tables II to VI) Most of the group believed that patients with bacterial endocarditis should be treated initially in the hospital and confined to bed during the early phase of their illness and

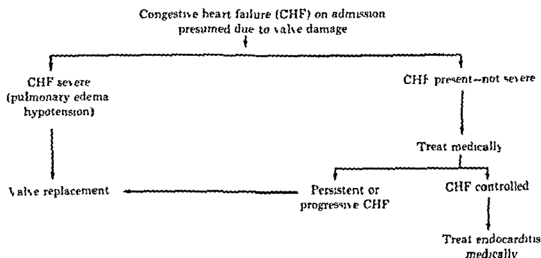
Table III Antibiotic treatment



that resumption of activity should be gradual The major complications included congestive heart failure arrhythmias renal failure anemia embolic phenomenon and mycotic aneurysms Congestive heart failure was thought to be the most serious complication (Table IV) especially if it was of sudden onset (either caused by obstruction of the valve in patients with natural valves or by paravalvular leak in patients with prosthetic valves) Earlier valve replacement was thought to be indicated by the group if a paravalvular leak was associated with endocarditis in a patient with a prosthetic valve The algorithm designed for patients with infectious endocarditis who present with systemic embolization (Table V) depends for its validity upon the accuracy of the echocardiogram and its interpretation Again if a prosthetic valve is involved surgical intervention is considered earlier

As expected those of us who reviewed the document were sometimes in disagreement This is in no way an adverse reflection on the individuals but simply points out the lack of definitive knowledge in this area One disagreement was whether trough (just before a dose of antibiotics) or peak (1 to 2 hours after a dose is completed) serum bactericidal levels should be used for *in vitro* determination of the adequacy of therapy (Obviously if a continuous infusion pump is used to administer an antibiotic there should be no peak or trough) Secondly it was questioned whether there is a need to determine serum bactericidal levels at all when treating a patient with a bacterium that has a minimum inhibitory

Table IV Surgical treatment of valvular bacterial endocarditis



bactericidal level of less than 0 1 µg/ml such as usually is the case with alpha hemolytic streptococcal disease Thirdly there was quite a bit of disagreement as to the appropriate agents for *Straphylococcus aureus* endocarditis Some believed that penicillin G should never be used because only a small percentage of strains are susceptible and testing might be difficult for small laboratories There was disagreement as to whether methicillin nafcillin or oxacillin was the best semisynthetic penicillin to use Although most felt that a daily blood culture should be obtained following the initiation of antibiotic therapy to determine whether the organism has been eradicated at least one reviewer felt that this might be unnecessary because the blood cultures would not be expected to be sterile in many instances until at least 2 or 3 days had passed My experience suggests that blood cultures will be sterile after 3 days of appropriate antibiotic therapy It was suggested that at the completion of the antibiotic therapy blood cultures should be obtained weekly for one month In my opinion this is of doubtful value in a patient who is asymptomatic Certainly the onset of fever makes it necessary to obtain blood cultures because relapse is clearly possible

Recurrence or relapse of bacterial endocarditis necessitates reevaluation and reinstitution of antibiotic therapy including retesting of antibiotic susceptibility of the bacterium involved consideration of valve replacement and possible extra sites of microbial persistence such as a splenic abscess (Table VI)

Although there was general agreement by the committee on the algorithms so much disagreement was evident when specific antibiotic therapy for specific microorganisms was considered that it was finally decided that it was not feasible to publish the antimicrobial therapy for infectious endocarditis The following recommendations regarding antibiotic treatment of specific types of endocarditis therefore represent my own preferences although I have tried to present more than one alternative to therapy

Antibiotic treatment of specific types of endocarditis

Alpha hemolytic streptococcal endocarditis Combined penicillin and streptomycin for the first two weeks of therapy followed by two weeks of penicillin G alone seems to be the most used and effective therapy with the least chance of relapse Some authors[10,11] recommend 4 8 million units of penicillin G per day given intravenous piggyback (1 2 million units every 6 hours) for 4 weeks with 1 gram of streptomycin (0 5 grams every 12 hours intramuscularly) daily for two weeks I prefer to use penicillin G by continuous infusion with a pump for four weeks adjusting the amount of penicillin depending on the serum bactericidal level (5 to 15 million units daily the usual dose) Unless there is overt nephrotoxicity and/or eighth cranial nerve problems I also use streptomycin for the first 2 weeks

Continuous intravenous infusion without the use of an infusion pump results in totally erratic serum levels Because the purpose of the penicillin is to eliminate bacterial growth my belief is

Table V Surgical treatment of valvular bacterial endocarditis

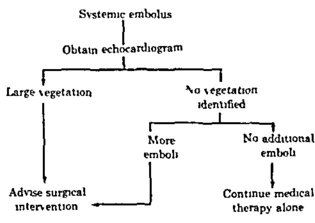
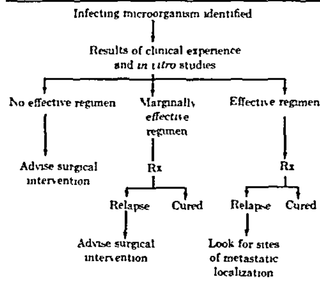


Table VI Antibiotic versus surgical treatment



that a continuous high level of penicillin G surrounding the vegetation will make it more effective than temporarily very high levels followed by a trough that reaches zero The intravenous site must be watched closely to avoid phlebitis A pediatric scalp vein needle is recommended and the infusion system should be changed every 72 hours

Patients allergic to penicillin may be treated with vancomycin alone (0 5 gm q 4 to 6 hr IBPB) for 3 weeks or if the reaction to penicillin was not an anaphylactic one with a cephalosporin administered with caution initially

Microaerophilic streptococci peptostreptococci (anaerobic streptococci) and other non D groupable streptococci are all treated in a fashion similar to alpha hemolytic streptococci

Group D streptococcal endocarditis Bacterial endocarditis due to nonenterococcus Group D streptococci such as *Streptococcus bovis* or *equinus* is treated in a fashion similar to alpha hemolytic streptococci with the exception that many would not use streptomycin for the first two weeks However recently endocarditis caused by *Streptococcus bovis* resistant to the lethal effect of penicillin alone has been reported [79]

Enterococcal endocarditis (group D streptococci of the enterococcus type [*Streptococcus faecalis* or *faecium*]) produces an especially refractory type of endocarditis Generally 20 to 40 million units of penicillin G per day given by infusion pump as a continuous intravenous drip for 6 weeks is indicated The dose of penicillin G may have to be adjusted depending on serum bactericidal levels Because of well-established synergism between streptomycin and penicillin G in activity against this organism I had recommended 1 gram of streptomycin intramuscularly or intravenously every 12 hours for the first 2 weeks therapy followed by 0.5 gm intramuscularly or intravenously every 12 hours for the next 4 weeks but now prefer gentamicin 3 to 5 mg /kg body weight/day depending on serum bactericidal levels for six weeks Gentamicin has been used successfully as a substitute for streptomycin and some studies suggest an increased synergism with penicillin Rahal' has published an excellent review on antibiotic combinations

Patients who are allergic to penicillin G may be given vancomycin (0.5 gm q 4 to 6 hr intravenous piggyback for 4 to 6 weeks) although the development of phlebitis usually limits how long this antibiotic can be given Ototoxicity is a problem but nephrotoxicity is not However it is advisable to get serum creatinine levels two to three times weekly when vancomycin is being administered for endocarditis because it is excreted by the kidneys Although minimum inhibitory concentrations of vancomycin may be achievable minimum bactericidal concentrations may be much higher Vancomycin and gentamicin appear to be synergistic for enterococci but both antibiotics are ototoxic Desensitization to penicillin may have to be performed and in some cases a vegetation may have to be surgically removed

even though the valve is not replaced Several good reviews on vancomycin have been published recently[8, 84] Vancomycin has also occasionally been useful in the therapy of other types of endocarditis One patient was reported to be cured with vancomycin after clindamycin had failed to eradicate a group B streptococcal endocarditis[8] Cephalosporins with or without aminoglycosides are not effective in the treatment of enterococcal endocarditis [1, 8]

Staphylococcus aureus endocarditis Endocarditis due to *Staphylococcus aureus* requires the use of penicillinase resistant penicillins such as methicillin nafcillin or oxacillin with the dose being at least 2 gm intravenously by the rapid infusion method every 4 hours for six weeks[70, 71] I prefer oxacillin because of the well recognized interstitial nephritis and cystitis associated with methicillin as well as an increasing number of reports of hepatotoxicity and bone marrow suppression (reversible) with nafcillin Even if the particular strain appears to be a nonpenicillinase producing one I use oxacillin because at least 80 per cent of the strains isolated in our hospital are resistant to penicillin G and a laboratory error with this particular organism would be disastrous Failure of response suggests either an oxacillin resistant or tolerant *Staphylococcus aureus* and vancomycin may be necessary *Staphylococcus aureus* may be tolerant to various antibiotics resulting in failure of response to a single agent[87] A combination of vancomycin with rifampin has been used successfully in such a patient who failed to respond to therapy that should have worked based on *in vitro* studies[89]

In the penicillin allergic patient a cephalosporin could be administered with the cautions previously mentioned I prefer to use cefazolin but opinions vary as to its use in the treatment of staphylococcal endocarditis[7, 71] because *in vitro* it is slightly more rapidly inactivated by *Staphylococcus aureus* beta lactamase than is cephalothin In man this inactivation is probably not important because of the dosage used (1 to 2 gm by rapid intravenous infusion every 4 to 6 hours) I have had uniformly successful results with the use of cefazolin and prefer it to the less reliably administered cephalothin which also is fairly rapidly metabolized in the liver Others have used cephalothin in a dose of 12 to 18 grams/day successfully[7] and continue to recommend it as the cephalosporin of choice If a patient has had an immediate type of hypersensitivity reaction to the penicillins then vancomycin in a dosage of 0.5 gm by rapid intravenous infusion every 4 to 6 hours would be the drug of choice I agree with Watanakunakorn that clindamycin a bacteriostatic antibiotic is undesirable for the treatment of staphylococcal endocarditis

Staphylococcal epidermidis endocarditis *Staphylococcal epidermidis* is the causative bacterium in some patients with prosthetic valve infections as well as in some patients who have congenital or valvular heart disease Such infections are frequently difficult to treat and often the valve must be removed in order to obtain a cure Many strains of *Staphylococcus epidermidis* that are resistant to the penicillins and cephalosporins may respond to vancomycin Recent information suggests that the combination of rifampin with either gentamicin nafcillin or vancomycin may be useful in treating this type of endocarditis as synergism apparently occurs[90]

Pneumococcal or Gonococcal Endocarditis Endocarditis caused by *Diplococcus pneumoniae* or *Neisseria gonorrhoeae* can be treated with penicillin G (10 to 20 million units per day by the continuous infusion route using an infusion pump for four weeks),[7, 71] Pneumococcal endocarditis usually results in aortic insufficiency due to aortic root and aortic valve ring involvement[7, 91, 92] and surgical treatment is frequently indicated Pneumonococcal meningitis and pneumonia often accompany the endocarditis Although gonorrhea has been rampant the classical gonococcal endocarditis patient with two spikes of temperature daily is rarely seen and I have not recognized a case in 15 years at Ochsner Clinic

Gram negative bacillary endocarditis Gram negative bacillary endocarditis is rare but is often associated with serious complications Monitoring the effectiveness of antimicrobial agents with serum bactericidal tests is controversial[70, 93, 8] but if done it is recommended that the bactericidal level be kept at a 1 8 dilution or higher My current recommendations for treating various gram negative bacillary endocarditis are given in Table VII[8] Frequently this type of infection requires surgical removal of the valve

An exciting discovery that may be of use in this particular type of endocarditis is the isolation of clavulanic acid a potent beta lactamase inhibiting compound derived from *Streptomyces clavuligerus* which is now available as sodium

clavulanate through the Beechum Laboratories[94] Recently *in vitro* studies have demonstrated that ticarcillin resistant *E coli Klebsiella pneumoniae Enterobacter* and *Proteus mirabilis* species were made susceptible with the addition of clavulanic acid[9] If this material proves to be as synergistic *in vivo* it may be of usefulness not only in the treatment of gram negative bacillary endocarditis but also in the treatment of staphylococcal endocarditis associated with beta lactamase production

Responses to therapy In the absence of complications a drop in temperature should occur within a few days to a week accompanied by conversion of blood cultures from positive to negative The patient should feel better and appetite should increase The erythrocyte sedimentation rate will fall and if the rheumatoid factor was positive initially it also should fall An insufficient course of antibiotic(s) will also bring about these changes but they will be transient If the patient is truly free from infection observation after the cessation of treatment will confirm it If relapse occurs it is usually within two to four weeks after the end of therapy Endocarditis in the same patient beyond that time usually represents reinfection

Other agents as adjuncts to antibiotic therapy Special problems arise in patients taking other drugs such as anticoagulant or fibrinolytic agents when endocarditis develops Since most authorities advise against the use of anticoagulants or fibrinolytic agents during endocarditis[9, 94] physicians usually stop the adjunctive therapy until the endocarditis can be brought under control However no well controlled studies have been conducted on the efficacy of antibiotic and anticoagulant therapy and the advice against it appears to be based on the reports mentioned earlier on the use of sulfonamides and anticoagulants[6, 66] The antimicrobial agent (sulfapyridine) worked poorly In addition the anticoagulants were of questionable quality and the methods for monitoring their use were not yet fully developed It was common practice to use sufficient anticoagulation to extend the clotting time from ½ to 1 hour and keep it at this level for up to two weeks or more[65, 6, 5]

When penicillin G became available initial studies of low dose penicillin G and heparin or dicumarol did not demonstrate much difference from earlier studies using sulfonamides and anticoagulants But as larger doses of penicillin with anticoagulants were used greater success rates were seen[5] However the older reports of the dangers involved with anticoagulant therapy remained and because penicillin G alone produced good success rates it became the rule not to use anticoagulants at all[104]

Table VII Antibiotic treatment of adults with endocarditis caused by gram negative bacilli*

Bacteria	*Drug/dosage*
Pseudomonas aeruginosa	Ticarcillin 18 g/day *plus* Tobramycin 3-5 mg/Kg BW/day
Enterobacteriaceae	Ampicillin 12 g/day *or* Ticarcillin 18 g/day *or* Cefazolin 4-8 g/day *plus* Gentamicin 3-5 mg/Kg BW/day or another aminoglycoside
Salmonella	Ampicillin 12 g/day *plus* Gentamicin 3-5 mg/Kg BW/day
Bacteroides fragilis	Ticarcillin 18 g/day *plus* Metronidazole 4 g/day†‡

*All antibiotics are administered intravenously
†Available for experimental use only from Searl Laboratories An intravenous form is available
‡See Galgiani, J N Busch, D F Brass C, et al. *Bacteroides fragilis* endocarditis, bacteremia and other infections treated with oral or intravenous metronidazole Am J Med 65 .34 1978.

Today however the concurrent use of anticoagulants is sometimes unavoidable in patients with prosthetic heart valves[1] in those with deep leg vein thrombosis or in those undergoing fibrinolytic therapy for pulmonary emboli At this institution we are currently reviewing the experience in treating those patients who were receiving anticoagulant therapy at the time of diagnosis of treatment of endocarditis

Some evidence suggests an efficacious role for anticoagulant and antibiotic treatment of bacterial endocarditis In an experimental model using rabbits Thorig and associates[105] and Hooke and Sande demonstrated a reduction in size of the valvular lesions when anticoagulant therapy was used In addition Hooke and Sande[9] showed that rabbits that were pretreated with anticoagulants had their endocarditis lesions cleared with antibiotics faster than rabbits having the antibiotic treatment alone Even if it could not be

proven that anticoagulant therapy is helpful in the treatment of bacterial endocarditis it would be extremely useful to know if it does indeed play any detrimental role

The role of fibrinolytic therapy as an adjunctive measure to antibiotic treatment of endocarditis also needs to be explored Work in rabbit and dog models has shown the possibility of reducing the size of the endocardial lesion with fibrinolytic drugs[110] Therefore the addition of aggressive antibiotic therapy to a carefully prepared fibrinolytic regimen may significantly shorten the treatment time of endocarditis as well as lessen the untoward secondary manifestations of the disease

Measures to decrease platelet numbers or function have not been effective in altering the course of the infection in experimentally produced endocarditis The use of aspirin to alter platelet function did not change the size of the endocardial lesion or the course of the infection[11] The administration of antiplatelet sera to induce thrombocytopenia has likewise failed to alter the localization of the organisms onto the valve lesion in the experimental rabbit model of endocarditis[109]

Conclusion

A paper that purports to summarize the prevailing opinions regarding a controversial subject such as the prophylaxis and therapy of bacterial endocarditis will obviously raise the eyebrows of readers who differ with the author I have no apologies for my choice of references or for my approach to the treatment of patients I welcome all comments that may help me improve the care of patients who are unfortunate enough to contract bacterial endocarditis

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Julian Frieden

Clinical pharmacology of the new beta-adrenergic blocking drugs Part 3 Comparative clinical experience and new therapeutic applications

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β adrenoceptor blocking drugs have proved efficacious in the treatment of angina pectoris hypertension and cardiac arrhythmias They have also shown clinical usefulness in the treatment of hypertrophic obstructive cardiomyopathies hyperthyroidism and pheochromocytoma Clinical studies have suggested an even broader range of newer potential indications migraine headache prophylaxis anxiety states schizophrenia tremor open angle glaucoma narcotic and alcohol withdrawal There is also a growing debate whether β adrenoceptor blocking drugs are useful in the therapy of acute myocardial infarction

There have been many reports of clinical trials involving thousands of patients most of which have dealt with propranolol the drug in clinical use the longest Clearly no two studies were done under the same conditions or with the same experimental design and the interpretation of their results is often difficult Additionally since so many physiological variables are affected by the β adrenergic system and hence its blockade the exact mode and nature of β blocking effect in different clinical entities is nearly impossible to precisely define However an *over all* impression of the efficacy of these agents can be derived from results of clinical trials and some of these results will be summarized for different pathophysiological states Some of the newer potential uses for β adrenoceptor blocking drugs will also be discussed

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Hypertension

There are several points to be noted in consideration of clinical trials with β blockers in hypertension

1 Patients may vary widely in individual dose requirements and rapidity of response Hence trials using small (or fixed) doses and short treatment periods may fail to show much effect

2 In double blind studies in which placebo follows active therapy the duration of placebo therapy must be long enough to allow blood pressure to rise to pretreatment levels If this is not done then the therapeutic benefit of active drug will appear to be modest

3 The best result of β blockers in hypertension is achieved when they are used in combination with other drugs especially diuretics

Propranolol (Inderal) There is a vast experience with the use of propranolol in hypertensive patients and hypertension is currently a U S Food and Drug Administration approved indication for its use Prichard and Gillam[1] using propranolol in a large number of patients previously treated with other antihypertensive regimens found that propranolol achieved the best control of supine blood pressure with the least side effects and the least postural hypotension The average daily dose used was 319 mg with a maximum dose of 4 000 mg /day Zacharias

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and co workers[3] studied 109 patients all of whom also received thiazide diuretics and obtained good results in about 60 per cent of their patients using an average dose of 290 to 320 mg /day (maximum 1 000 mg /day) Only 20 per cent of the patients required more than 600 mg /day Other double blind trials in propranolol responders have shown a significant difference between drug and placebo[3]

In a double blind study of Jamaican blacks with hypertension Humphreys and Delvin[4] using lower doses of propranolol (maximum 360 mg /day) without diuretics demonstrated far less satisfactory results (This study raised the question of whether there is a decreased sensitivity of blacks to the effects of β blockade compared to whites)

In general propranolol is now very widely used in hypertension Its large usage in the United States even prior to FDA approval for its use in hypertension testifies to the recognition of its efficacy by the medical community Although generally effective it frequently requires a high dosage sometimes in the grams range

Practolol (Eraldin) Practolol the first cardiospecific β blocker has had widespread clinical use It has fairly potent intrinsic sympathomimetic activity but has no membrane stabilizing activity Many studies[5] have shown clinically significant reductions in blood pressure and its cardioselectivity made it useful in patients felt to be at risk for developing asthma The recognition of major toxic effects of practolol has led to its withdrawal and the results of clinical trials will not be discussed further here

Oxprenolol (Trasicor) Oxprenolol is a nonselective β blocker with partial agonist activity (intrinsic sympathomimetic activity ISA) and less membrane effect than propranolol Leishman and colleagues studied the effect of oxprenolol in 14 patients In a double blind comparison between placebo and oxprenolol (320 mg /day average) there was a significant reduction in supine and standing blood pressure with oxprenolol without significant side effects Tuckman in a study of 17 patients using an average daily dosage of 374 mg /day of oxprenolol (range 60 to 600 mg) also demonstrated reduction in systolic pressure without development of postural hypotension[11] Muiesan and associates[2] were able to demonstrate a dose related antihypertensive effect for oxprenolol at much lower dosages (20 to 80 mg /day) when used in conjuction with hydrochlorthiazide and dihydralazine Oxprenolol is equipotent milligram for milligram with propranolol

Alprenolol (Aptin) Alprenolol is a non selective β blocker with partial agonist activity (ISA) and some membrane activity Tibblin and Åblad[11] in a double blind crossover comparison between alprenolol (up to 400 mg /day) and placebo in 1[illegible] patients found significant reductions in supine and standing blood pressures with alprenolol compared with placebo or control Vedin[14] and co workers found alprenolol 400 to 800 mg /day to be more effective than methyldopa 750 to 1500 mg /day Bengtsson[15] performed a double blind comparison between alprenolol (150 to 300 mg three times a day) and propranolol (60 to 120 mg three times a day) in mild hypertensives he found the two drugs to be equivalent but there was less slowing of heart rate with alprenolol In another double blind crossover comparison of alprenolol (400 mg /day) and propranolol (60 mg /day) no significant difference could be demonstrated[16] Chlorthalidone plus alprenolol (400 to 800 mg /day) and chlorthalidone plus methyldopa (750 to 1500 mg /day) produced similar beneficial effects in blood pressure reduction but there were more severe side effects with methyldopa[17] Over all alprenolol is very similar to oxprenolol and propranolol

Pindolol (Visken) Pindolol (prindolol) will be discussed in greater detail in a subsequent article in this series It has very little membrane activity and some possible peripheral vasodilator effects However most prominent is its considerable intrinsic sympathomimetic activity which may explain the paradoxical loss of blood pressure control seen in some patients in high dosages

Pindolol is milligram for milligram the most potent of the beta blocking drugs Several series have demonstrated good often striking responses in blood pressure control some at comparatively low doses[8] In one trial of Waal Manning and Simpson[9] nearly all of 43 patients who were switched from other therapy to pindolol had improved BP control with an average dose of about 15 mg daily Several other studies have also demonstrated clinically useful antihypertensive effects[8] Pindolol has a longer duration of action than propranolol and can be given twice or even once daily with successful results

Sotalol (Betacardone Sotacor) Sotalol is a

non cardioselective β blocker, without partial agonist activity (ISA) or membrane effect It is effective in lowering blood pressure and it is well tolerated Because of its long half life (9 5 hours) it need only be given twice daily Sundquist and colleagues[4] found that on a weight basis it is significantly less potent than propranolol with an effect on BP that is closely dose related in doses of 200 to 600 mg /day

Timolol (Blocadren) Timolol is a non cardioselective β blocker with no intrinsic sympathomimetic or membrane stabilizing activity (similar to sotalol) Dose for dose it is about six times more potent than propranolol It appears to be as effective an hypotensive agent as propranolol and the recommended dose is 15 to 45 mg /day [1, 2]

Acebutolol (Sectral) Acebutolol has partial agonist activity and membrane stabilizing effect Although in animal studies it acts as a selective β blocker this has not been a general finding in man It appears to be an effective antihypertensive agent in doses up to 1 000 mg /day [23]

Atenolol (Tenormin) Atenolol is a cardioselective β blocker with no intrinsic sympathomimetic activity or membrane stabilizing activity It has a comparatively long half life 6 hours In a series of 43 patients using 100 mg of atenolol twice daily Hansson and co workers[24] were able to demonstrate excellent BP responses with little side effects They were able to confirm these initial results in a subsequent double blind comparison with placebo In a series of 37 patients treated with atenolol Meekers and associates[26] found good results in almost all their patients with little added benefit to be gained by doses higher than 300 mg /day

Metoprolol (Betaloc Lopresor) Metoprolol is a new cardioselective β blocker without intrinsic sympathomimetic or membrane effect In several studies [28] it has been shown to be an effective well tolerated antihypertensive agent It has recently been approved for use in hypertension by the United States Food & Drug Administration

Efficacy of β blockers in hypertension

The β blockers differ in terms of presence or absence of intrinsic sympathomimetic activity membrane effect cardioselectivity and in terms of relative potencies and durations of action It is unclear whether these differences have any practical relevance in the clinical treatment of hypertension *all* β blockers to date have antihypertensive effects Three points however can be made (1) drugs with intrinsic sympathomimetic activity (partial agonist activity) cause less bradycardia (2) presence or absence of membrane stabilizing effect seems to be irrelevant (3) if a beta blocker has to be given to a potential asthmatic it is best to use a cardioselective β blocker or one with ISA (It must be cautioned however that as dosage increases cardioselectivity diminishes)

Angina pectoris

There is now no question about the effectiveness of beta adrenergic blockade in angina pectoris The greatest experience has been reported with propranolol however therapeutic trials with other β blocking agents have also shown them to be effective prophylactics Although this paper will not deal with the differences in clinical trial designs it should be borne in mind that variations in design (run in periods fixed vs variable dosage schedules duration of assessment period acute vs chronic administration etc) may be responsible for differences in results obtained

Propranolol (Inderal) There have been many trials of propranolol (membrane stabilizing activity no ISA non selective) with differing daily dosages that have demonstrated its effectiveness The clinical efficacy of propranolol in angina is well known and the results of clinical trials have been summarized by other authors [29]

A dose dependent reduction of anginal attacks with propranolol was well demonstrated in a study by Prichard and Gillam [3] Sixteen patients were administered four different dose levels of propranolol and placebo for a period of 2 weeks each in a double blind fashion The average doses ranged from zero (placebo) to 417 mg per day The initial study was repeated twice thereby each patient receiving each treatment for six weeks As dosage increased there was a progressive decrease in the number of anginal attacks and in the amount of nitroglycerin used giving a linear dose response curve whose slope did not flatten even at the 417 mg dosage level (suggesting that maximum effect had not yet been obtained) Thus if side effects do not intervene patients can be expected to respond better on higher doses of propranolol than on lower doses

Oxprenolol (Trasicor) (Membrane stabilizing activity intrinsic sympathomimetic activity non cardioselective) In a fixed dosage (80 mg -3 times per day) trial of oxprenolol Sandler and

Pistevos[31] failed to show a significant effect in 13 patients in frequency of angina attacks or a difference in exercise tolerance Bianchi and co workers[3] in 62 patients using a fixed dosage of 40 mg four times per day demonstrated a decrease in frequency of angina and in nitroglycerin consumed Both these studies used 2 week assessment periods and lacked proper run in periods (the run in period prior to the trial period proper provides time during which patients become familiar with the experimental protocol and during which drug dosage can be adjusted) Wilson and colleagues[33] performing a 2 week trial using a variable dose schedule (60 to 400 mg oxprenolol/day) that was preceded by a run in period demonstrated a significant benefit, with 17 of 18 patients having less angina with oxprenolol

Alprenolol (Aptin) (Membrane stabilizing activity intrinsic sympathomimetic activity non cardioselective) Wasserman and co workers[34] studying nine patients and using 4 weeks of treatment with 160 mg or 400 mg /day of alprenolol failed to show a significant effect on anginal frequency or exercise tolerance This trial did not have an adequate run in period Aubert and associates[1] using a fixed dose of 100 mg alprenolol 4 times/day demonstrated a significant reduction in frequency of anginal attacks in 18 patients Hickie using an 8 week run in period in 50 patients in a multicenter trial demonstrated a 33 per cent reduction in the number of attacks and nitroglycerin consumed with alprenolol compared with placebo In a fixed multidose study Sowton and Smithen obtained an increase in exercise tolerance with doses of 100 mg 200 mg and 400 mg alprenolol twice daily Although no dose-response relationship was demonstrated this may reflect the design of the clinical trial (i e the administration of increasing drug dosages was not random) and is not conclusive

Heatherington and colleagues[38] compared fixed doses of alprenolol (400 mg /day) and propranolol (160 mg /day) in 26 patients Although there was increased exercise tolerance with both drugs they both failed to provide a significant difference in frequency of anginal attacks and nitroglycerin consumption compared with placebo

Pindolol (Visken) (Has intrinsic sympathomimetic activity no membrane stabilizing effect non cardioselective) Several double blind studies have demonstrated that pindolol in a dose of 10 mg daily effected a greater decrease in anginal attacks and nitroglycerin consumption than placebo Further discussion of pindolol including results of our studies will be presented in a later article in this series

Sotalol (Betacardone Sotacor) (No intrinsic sympathomimetic activity no membrane stabilizing activity non cardioselective) In a fixed multidose level (80 160 320 640 1 280 mg sotalol/day) trial in nine patients Toubes and co-workers[39] demonstrated a significant decrease in frequency and severity of anginal attacks and a reduction in nitroglycerin consumption at all dose levels In a variable oral dose trial comparing sotalol with propranolol Horn and Prichard found propranolol (avg 746 mg /day) to be more effective than sotalol (avg 786 mg /day) However this dose of sotalol was significantly better than low dose propranolol (avg 93 mg /day)

Timolol (Blocarden) (No membrane stabilizing activity, no ISA non cardioselective) Brailovsky[41] using an average dose of 30 mg timolol in a large multicenter trial in 307 patients found a highly significant reduction in the frequency of anginal attacks compared with placebo

Acebutolol (Sectral) (Has partial agonist activity and membrane stabilizing effect acts as a selective β blocker in animals ? in man) Khambatta[42] found acebutolol more effective than propranolol in a trial of 25 patients with angina pectoris However since the dose of propranolol used in most of these patients was probably suboptimal (80 mg /day) it is difficult to draw firm conclusions from the study

Practolol (Cardioselective with ISA) Practolol was the first cardioselective β receptor antagonist developed While used it was found to be effective in angina pectoris Because of increased recognition of toxic effects practolol has been withdrawn from use and reports of clinical trials will not be discussed further here However in the past years other cardioselective β blockers have been developed

Atenolol (Atenol Tenormin) (Cardioselective no ISA) Astrom and Vallin[43] compared atenolol and propranolol 5 mg intravenously in ten patients with severe angina Both agents caused an equal reduction in exercise induced tachycardia Maximal work capacity was higher with atenolol this may be related to its cardioselectivity and therefore lack of interference with the

peripheral vascular response to exercise It was also observed that atenolol was associated with a slight increase in airway conductance compared with the reduction produced by propranolol (This too may reflect cardioselectivity) Roy and co workers[4] in a trial of 11 patients with severe angina, found that atenolol in oral doses of 50 100 and 200 mg twice daily produced a significant reduction in anginal attacks and nitroglycerin consumption when compared with placebo A dose–response relationship was also suggested by their results There was some increase in exercise tolerance with atenolol that was not statistically significant

Metoprolol (Betaloc Lopressor) (Cardioselective no ISA) Adolfsson and colleagues[43] in 17 patients given 40 mg metoprolol orally demonstrated a 42 per cent increase in acute exercise tolerance Other data also seem to indicate that metoprolol is an effective antianginal agent

It appears that beta blockers when initiated at low dosage and when the contraindications of asthma and congestive heart failure are observed are a safe and effective prophylaxis against angina pectoris Although pain is usually not totally relieved the frequency of attacks is reduced and more pain free exercise can be accomplished Failure of chest pain to respond to β blocking drugs may be due to (1) poorly controlled heart failure with cardiac enlargement (2) misdiagnosis of angina or (3) inadequate dosage There is also some evidence though not yet conclusive that long term β blockade improves prognosis with some studies showing a decrease in mortality rate and rate of infarction

Arrhythmias

Beta blocking drugs have become an important mode of treatment of various cardiac arrhythmias A discussion of their possible modes of action appeared in an earlier article in this series Before discussing results of studies with some of these agents some general aspects of the individual arrhythmias in which β blockade may have a role will be addressed In general β blockers have been more effective in the treatment of supraventricular than ventricular arrhythmias

Supraventricular arrhythmias These respond variably to β blockade They may often be as useful diagnostically as therapeutically by slowing a very rapid heart rate they sometimes will allow for the establishment of an accurate ECG diagnosis of an otherwise puzzling arrhythmia

Sinus tachycardia This arrhythmia usually has an obvious cause (e g fever hyperthyroidism congestive heart failure etc) and therapy should address itself to correction of the underlying condition If the sinus tachycardia should require direct intervention β blockade is effective therapy

Supraventricular ectopics Again treatment is seldom required and usually is addressed to the underlying cause These often herald the onset of atrial fibrillation and there is no evidence to show that β blockade can prevent this development When due to digitalis toxicity however, supraventricular ectopic beats generally respond well to β blockade

Paroxysmal supraventricular tachycardia (SVT) These may be divided into two groups (1) those related to abnormal conduction (e g reciprocating AV nodal tachycardia the re-entry tachycardias as in Wolff Parkinson White syndrome in which there is abnormal conduction through an AV nodal bypass pact) and (2) those caused by ectopic atrial activity—as in digitalis toxicity Since β blockade prolongs AV conduction (A H interval is increased in His bundle electrograms) and prolongs the refractory period of the re entrant pathways, it is no surprise that many cases of SVT respond to β blockers In acute episodes vagal maneuvers after β blockade may be effective in terminating the arrhythmia where they were unsuccessful before β blockade In addition if sinus rhythm is still not restored the use of β blocking drugs still leaves the option of direct current countershock cardioversion an option not safely available if digitalis is used initially

Atrial flutter β blockade can be used to slow the heart (by increasing AV block) and may restore sinus rhythm This is a situation in which β blockade may be of diagnostic value given intravenously β blockers slow the ventricular response and permit the differentiation of flutter waves ectopic P waves or a sinus mechanism

Atrial fibrillation The major action of β blockers here is the reduction in ventricular response by increasing the refractory period of the AV node All β blocking drugs have been effective in slowing ventricular rates in patients with atrial fibrillation However they are less effective than quinidine or DC cardioversion in the reversion of

atrial fibrillation to sinus rhythm (although this can occur especially when the atrial fibrillation is of recent onset) These drugs must be used cautiously when atrial fibrillation occurs in the setting of a severely diseased heart that is dependent on high levels of adrenergic tone to avoid failure β blockers may be particularly useful in controlling the ventricular rate in situations when this is difficult to achieve with maximum tolerated doses of digitalis Examples are thyrotoxicosis and hypertrophic cardiomyopathy

Ventricular arrhythmias β blocking drugs can abolish or decrease the frequency of ventricular ectopic beats in various cardiac conditions They are particularly useful if these arrhythmias are related to catecholamines (exercise pheochromocytoma halothane anesthesia exogenous administration of catecholamines) or digitalis However it has not been shown that this reduces the incidence of sudden death from ventricular arrhythmia in patients at risk

Ventricular tachycardia and fibrillation Beta blocking drugs should not be considered agents of choice in acute cases of ventricular tachycardia Cardioversion or other antiarrhythmic drugs (lidocaine quinidine pronestyl etc) should be the initial agents of therapy β blockers have however been shown to be of benefit in prophylaxis against recurrent ventricular tachycardia particularly if sympathetic stimulation appears to be a precipitating cause There have been many reported cases of prevention of exercise induced ventricular tachycardia with β blockers in many of which there was a poor response to digitalis or quinidine [50]

In ventricular fibrillation although the immediate therapy is electrical defibrillation intravenous administration of β blocking drugs (in combination with lidocaine or pronestyl) may often be effective in preventing recurrences [51, 52]

As has been mentioned in a preceding article [53] the effectiveness of β blocking agents in arrhythmia seems to be related to cardiac β adrenoreceptor blockade Therefore *all* β blockers would be expected to be therapeutically effective in arrhythmias If there is to be a preference for a given β blocker in a specific situation it would relate to its ease of administration the likelihood of side effects and the presence or absence of other associated properties (e g partial agonist activity cardioselectivity)

Propranolol (Inderal) The efficacy of propranolol in the therapy of many cardiac arrhythmias is well established Dosages of 80 to 100 mg four times daily during chronic administration are likely to produce plasma levels of 40 to 85 mg/ml or higher—a level that should be adequate for control of arrhythmias [54, 55] Occasionally doses as low as 10 mg four times daily will provide good therapeutic results therefore it is reasonable clinical practice to start patients on a lower dosage regimen and gradually increase the dose until a satisfactory result is obtained

Propranolol must be given cautiously by the intravenous route especially when heart failure is present One safe method is to give 0 5 to 0 75 mg every 2 minutes until the desired response is obtained or until a total dose of 0 1 mg/Kg has been given Blood pressure the electrocardiogram and signs of congestive heart failure should be monitored and watched for and atro[isoproterenol and a temporary intravenous p maker wire should be available for use if br cardia AV block or asystole should develop

Alprenolol (Aptin) Alprenolol is simila propranolol in that it possesses compar β blocking and membrane stabilizing activit differs from propranolol in that alprenolol significant intrinsic sympathomimetic act (ISA partial agonist activity) Because of its alprenolol does not depress resting heart ra atrioventricular conduction as much as prop olol and may also provide less cardiac depres activity making it a potentially safer drug for in impaired myocardial function [5] An oral dos 40 mg of propranolol has an approximately e β blocking effect as does 100 mg of alp olol Intravenously the two drugs are app imately equipotent milligram for m gram

Many clinical studies have shown that anti arrhythmic profile of alprenolol is simila propranolol [56, 57, 60] Fifty mg every 6 hours reasonable initial oral dose which can increased gradually to 100 mg or more ever hours until clinically adequate β blockade achieved (A sustained release [200 mg tab preparation of alprenolol may be easier to adm ister and can be given every 12 hours) For ac therapy alprenolol can be given intravenousl a rate of 1 mg per minute until the des response is achieved or to a total of 20 m Careful monitoring should be maintained as w propranolol In one series of 15 patients w

acute myocardial infarction four patients given alprenolol intravenously (2 5 to 5 mg) developed sudden circulatory collapse and clinical shock[61]

Oxprenolol (Trasicor) Oxprenolol has about an equivalent β blocking potency as propranolol has less membrane stabilizing effect and has significant partial agonist activity (intrinsic sympathomimetic activity) It has been used orally and intravenously in controlling cardiac arrhythmias [61] and can be used in a similar fashion as alprenolol In acute therapy of arrhythmias it may be given at a rate of one mg /minute up to a dose of 12 mg using the previously described precautions (Some authors have used up to 30 mg safely[63]) Twenty mg every 6 hours appears to be a reasonable initial oral dose which can be gradually increased as needed

Pindolol (Visken) This β blocker is being intensively evaluated and details will be discussed in a subsequent article in this series On a weight for weight basis pindolol has been found to be from four to 40 times as potent a β adrenoreceptor blocker as propranolol It has very little membrane stabilizing activity but has significant intrinsic sympathomimetic activity and therefore will not depress resting heart rate as much as propranolol will

Plasma levels effective in controlling arrhythmias (20 to 40 ng /ml) can be achieved by oral doses of 5 mg pindolol every 6 to 8 hours[64] which provides antiarrhythmic activity similar to that of propranolol [5] An intravenous total dose of 0 2 to 1 0 mg of pindolol is equivalent to 1 to 5 mg of intravenous propranolol and provides an effective regimen for acute therapy A dosage of 5 to 10 mg every 6 hours appears to be a suitable maintenance form of chronic oral therapy

Practolol (Eraldin) Practolol is a cardioselective β antagonist and was therefore felt to be a β blocker of choice in patients with obstructive airway disease (Cardioselectivity however is relative and decreases with larger doses which can therefore cause airway obstruction in some patients)[66] Practolol like propranolol has established value in the treatment of many cardiac arrhythmias[67,69] Practolol has however been withdrawn from use because of serious toxic side effects and will not be discussed further here

Sotalol (Betacardone Sotacor) Sotalol is a non cardioselective β blocker without intrinsic sympathomimetic activity It has no membrane stabilizing activity and has little myocardial depressant action The antiarrhythmic spectrum of sotalol is similar to propranolol practolol or oxprenolol in doses up to 20 mg intravenously[63,67,7,72] Sotalol may be a particularly useful agent in controlling arrhythmias related to elevated sympathetic activity—e g thyrotoxicosis—because it lacks intrinsic sympathomimetic properties

Timolol (Blocadren) Timolol which has no intrinsic sympathomimetic or membrane stabilizing activity is about five to 10 times as potent as propranolol in man It seems to have antiarrhythmic effects comparable to those of propranolol

Acebutolol (Sectral) Although it acts as a selective β blocker in animals this has been a variable finding in man It possesses significant membrane stabilizing activity Lewis and associates[73] have shown an antiarrhythmic spectrum for acebutolol similar to practolol but acebutolol seems to have more myocardial depressant effect

Atenolol (Tenormin) Atenolol is cardioselective but differs from practolol in that it lacks intrinsic sympathomimetic activity It has no membrane stabilizing activity and about half the β blocking potency of propranolol

Metoprolol (Betaloc Lopresor) another cardioselective agent is very similar to atenolol

Newer applications of beta adrenoceptor agents

Beta adrenoceptor blockers in hyperthyroidism The role of the adrenergic nervous system in producing the features of thyrotoxicosis remains uncertain Many of the features of the disease do resemble the effects of sympathetic stimulation and can be ameliorated although not totally abolished by spinal anesthesia and ganglion blockade In recent years these observations have been extended to include the effect of beta adrenoceptor antagonists[7] The results obtained have been conflicting It is still not established whether the increased adrenergic activity is related to increased levels of catecholamines or altered receptor sensitivity[7,77] It is also possible at least in the heart that the changes might be attributed to a direct effect of thyroxine[5] whose own non specific effectors (adenylate cyclase system) are separate from those of cardiac beta receptors

Despite the failure to elucidate precisely the relationship between hyperthyroidism and cate

cholamines the apparent clinical connection has resulted in attempts to induce sympathetic blockade as part of the management of the disease for many years Sympatholytic drugs guanethidine and methyldopa were first used and subsequently pronethalol the first β adrenoceptor blocking drug was given to patients with spontaneous hyperthyroidism all without much apparent useful effect[80] However propranolol was shown to reduce resting heart rate significantly in hyperthyroid patients and subsequent β blocking drugs are being extensively investigated in this disease[81]

The exact mechanism of beta blockers in hyperthyroidism is not fully defined It is not known whether the effects of beta blockers are mediated through an adrenergic blockade mechanism or as has recently been suggested by blocking the peripheral conversion of T_4 to T_3[8]

Particular benefit has been obtained with beta blocking in the management of thyrotoxic crises (thyroid storm)[83] Beta blockade produces a rapid reduction in fever, tachycardia and central effects such as restlessness and disorientation Most of the experience to date with beta blockers in thyroid storm has been reported with propranolol[84] Beta blockers have also been used as a preoperative medication in thyrotoxic patients undergoing partial thyroidectomy[85]

As part of the routine medical management beta blocking drugs are of less certain value All are capable of reducing heart rate although pronethalol oxprenolol alprenolol practolol and pindolol (all of which possess intrinsic sympathomimetic activity) are less effective than those agents without this property (such as propranolol and sotalol) Other manifestations of the disease such as tremor hyperreflexia agitation hemodynamic changes hyperkinesia and those eye signs attributable to sympathetically innervated smooth muscle all may be reduced by propranolol practolol sotalol and pindolol[86-90]

β blockade in thyrotoxic patients has no effect on either thyroid hormone secretion the peripheral disposal of thyroxine or the thyrotropic and prolactin responses to thyrotropin releasing hormone Patients fail to gain weight satisfactorily despite an improved nitrogen balance and evidence of increased metabolism persists[78, 87, 8] β blockers cannot be considered as long term substitutes for specific antithyroid therapy

In establishing the role for β blockers in hyperthyroidism drugs with intrinsic sympathomimetic activity are effective in reducing the peripheral manifestations of hyperthyroidism but they are less effective than drugs without intrinsic sympathomimetic activity, particularly with respect to control of tachycardia Further experience has not confirmed the early contention that drugs with intrinsic sympathomimetic activity might be responsible for precipitating arrhythmias in hyperthyroid patients and might, therefore be dangerous[94]

Beta adrenoceptor blocker therapy in hypertrophic cardiomyopathy Beta adrenoceptor blocking drugs have proved to be efficacious in the therapy of patients with hypertrophic cardiomyopathy or idiopathic hypertrophic subaortic stenosis (IHSS)[9, 96] These drugs are useful in controlling the symptoms dyspnea angina and syncope[97] They also have been shown objectively to lessen the intraventricular pressure gradient both at rest and with exercise

The outflow pressure gradient is not the only abnormality in hypertrophic cardiomyopathy more important is the loss of ventricular compliance which impedes left ventricular function It has been shown by invasive and noninvasive methods that both propranolol and practolol improve left ventricular function[98] Both drugs produce favorable changes in ventricular compliance and reduction of angina and palpitations

The long term hemodynamic effects of beta blockers have not been established but since these agents have such a beneficial effect on impaired ventricular compliance they may frequently influence the natural history of the disease

There has been limited experience except for anecdotal situations with the other beta blockers (other than practolol) in therapy of hypertrophic cardiomyopathy However one might suspect that an agent with intrinsic sympathomimetic activity might be less efficacious than beta blockers without this property This was suggested by a lesser improvement with practolol compared to propranolol in a comparative study of patients with hypertrophic cardiomyopathy[99]

Beta adrenoceptor blocker therapy in myocardial infarction Although there is evidence that administration of beta adrenoceptor blocking agents shortly after the onset of acute myocardial

infarction might decrease the amount of ischemic injury in selected individuals the drugs precise roles in the treatment and prophylaxis of acute myocardial infarction and its recurrence is controversial and requires additional research and study

Newer therapeutic indications for beta blockers

Migraine prophylaxis Several studies have demonstrated the prophylaxis efficacy of pro pranolol for migraine headache[99, 100] About a third of the patients in these studies showed dramatic improvement in frequency and severity of attacks along with a significantly reduced need for ergotamine and analgesic medication Another third of the patients showed moderate improvement and the remainder showed no response to propranolol therapy Recently pro pranolol was approved by the Food and Drug Administration for migraine headache prophylaxis

Inhibition of peripheral vasodilation is the likely reason for the beneficial effect of propranolol in migraine Pindolol and alprenolol perhaps because of their partial agonist activity have shown little or no effect in migraine[101]

Tremor There is some evidence that heightened adrenergic activity may play a role in some varieties of tremor[102, 103] Propranolol is reported ly useful in the treatment of action tremors including essential familial and senile tremors and familial essential myoclonus[104-106] Most of the patients with benign action tremors noted clinical improvement with 60 to 240 mg of oral propranolol daily A few patients showed virtually complete resolution of the tremor while the majority of the patients reported mild improvement The best responses were obtained in younger patients who had shorter histories of tremor In one long term study the drug did not prevent the gradual progression of essential tremor but clinical improvement was still apparent after 2 to 4 years of continuous propranolol treatment

There are as yet no good clinical studies using the newer beta blocking drugs for treatment of tremor Whether or not non selective beta blockers will prove more efficacious than those with cardioselectivity has yet to be determined

Anxiety Granville Grossman and Turner[107] first suggested that beta blocking drugs might be of value in treating anxiety Since that time several studies have appeared and most of them have been reviewed by Whitlock and Price[108] The studies over all are rather inconclusive even when the investigators utilize a satisfactory double blind protocol It was found that patients derived benefit from propranolol only if they presented initially with dominant somatic com plaints (palpitations shakiness tremor) as opposed to psychic symptoms β blockers affect the physiological consequences of anxiety proba bly by blockage of the peripheral feedback loop of sympathetically mediated responses[1]

Non cardioselective beta blockers (propranolol alprenolol) might be more useful in anxiety states than drugs with cardioselectivity (which do not block peripheral receptors) or intrinsic sympathomimetic activity (which activate peripheral receptors) However this has not yet been tested in clinical trials

Schizophrenia The use of beta adrenoceptor blocking drugs in this area is highly controversial[109, 110] Several studies have appeared that describe the use of propranolol (up to 5800 mg/day) in schizophrenic patients[111, 112]

In general favorable results have been claimed in patients with acute psychotic states while chronically affected patients do not seem to respond The beneficial response to beta blockade becomes apparent sometimes within hours[11]

Despite the initial excitement generated by the apparent usefulness of beta blockers in acute psychosis none of the clinical trials were based on double blind design The possibility of spontaneous clinical remission and the concomitant use of other anti psychotic drugs were not taken into consideration[113] The possible mechanism for a beta blocker response in patients with acute schizophrenia has also not yet been elucidated If it relates to a central nervous system effect those drugs which rapidly cross the blood-brain barrier (alprenolol propranolol) might prove more efficacious than beta adrenoceptor blocking agents which do not demonstrate this property

Narcotic and alcohol withdrawal Anecdotal reports suggest that propranolol reduces heroin induced euphoria ameliorates narcotic abstinence syndromes and may be useful in treating narcotic addiction[11, 1] However no adequate clinical trials have been conducted with propranolol or the other new beta adrenoceptor blocking agents in treating narcotic addiction and the effectiveness of these drugs in this condition is questionable

cholamines, the apparent clinical connection has resulted in attempts to induce sympathetic blockade as part of the management of the disease for many years Sympatholytic drugs, guanethidine and methyldopa were first used and subsequently, pronethalol the first β adrenoceptor blocking drug was given to patients with spontaneous hyperthyroidism all without much apparent useful effect [9] However, propranolol was shown to reduce resting heart rate significantly in hyperthyroid patients and subsequent β blocking drugs are being extensively investigated in this disease [8]

The exact mechanism of beta blockers in hyperthyroidism is not fully defined It is not known whether the effects of beta blockers are mediated through an adrenergic blockade mechanism or as has recently been suggested by blocking the peripheral conversion of T_4 to T_3 [8]

Particular benefit has been obtained with beta blocking in the management of thyrotoxic crises (thyroid storm) [83] Beta blockade produces a rapid reduction in fever tachycardia, and central effects such as restlessness and disorientation Most of the experience to date with beta blockers in thyroid storm has been reported with propranolol [84] Beta blockers have also been used as a preoperative medication in thyrotoxic patients undergoing partial thyroidectomy [85]

As part of the routine medical management beta blocking drugs are of less certain value All are capable of reducing heart rate although pronethalol oxprenolol alprenolol practolol *and pindolol (all of which possess intrinsic sympa*thomimetic activity) are less effective than those agents without this property (such as propranolol and sotalol) Other manifestations of the disease such as tremor hyperreflexia agitation hemodynamic changes hyperkinesia and those eye signs attributable to sympathetically innervated smooth muscle all may be reduced by propranolol practolol sotalol and pindolol.[85, 90]

β blockade in thyrotoxic patients has no effect on either thyroid hormone secretion the peripheral disposal of thyroxine or the thyrotropic and prolactin responses to thyrotropin releasing hormone [9] Patients fail to gain weight satisfactorily despite an improved nitrogen balance and evidence of increased metabolism persists β blockers cannot be considered as long term substitutes for specific antithyroid therapy

In establishing the role for β blockers in hyperthyroidism, drugs with intrinsic sympathomimetic activity are effective in reducing the peripheral manifestations of hyperthyroidism but they are less effective than drugs without intrinsic sympathomimetic activity particularly with respect to control of tachycardia Further experience has not confirmed the early contention that drugs with intrinsic sympathomimetic activity might be responsible for precipitating arrhythmias in hyperthyroid patients and might therefore be dangerous [94]

Beta adrenoceptor blocker therapy in hypertrophic cardiomyopathy Beta adrenoceptor blocking drugs have proved to be efficacious in the therapy of patients with hypertrophic cardiomyopathy or idiopathic hypertrophic subaortic stenosis (IHSS) [95, 96] These drugs are useful in controlling the symptoms dyspnea angina and syncope [97] They also have been shown objectively to lessen the intraventricular pressure gradient both at rest and with exercise

The outflow pressure gradient is not the only abnormality in hypertrophic cardiomyopathy more important is the loss of ventricular compliance which impedes left ventricular function It has been shown by invasive and noninvasive methods that both propranolol and practolol improve left ventricular function [98] Both drugs produce favorable changes in ventricular compliance and reduction of angina and palpitations

The long term hemodynamic effects of beta *blockers have not been established but since* these agents have such a beneficial effect on impaired ventricular compliance they may frequently influence the natural history of the disease

There has been limited experience except for anecdotal situations with the other beta blockers (other than practolol) in therapy of hypertrophic cardiomyopathy However one might suspect that an agent with intrinsic sympathomimetic activity might be less efficacious than beta blockers without this property This was suggested by a lesser improvement with practolol compared to propranolol in a comparative study of patients with hypertrophic cardiomyopathy [8]

Beta adrenoceptor blocker therapy in myocardial infarction Although there is evidence that administration of beta adrenoceptor blocking agents shortly after the onset of acute myocardial

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Primary secondary or tertiary

These words have crept into medical terminology slowly and have various connotations. In hyperparathyroidism they represent a concatenation of causes in the latter two terms, whereas primary hyperparathyroidism is caused by an apparently autonomous tumor of one of the glands.

In the so-called "delivery of medical care" a term dear to epidemiologists who do not deliver any personally but study how it is done or how it should be done the terms "primary" "secondary" and "tertiary" have also crept into the vocabulary but have an entirely different meaning. As I understand it, primary care is largely preventive and includes such things as immunization well baby examinations yearly checkups, and the treatment of asymptomatic conditions such as early hypertension late onset diabetes mellitus and hyperlipidemia.

Secondary care would, I believe include the treatment of symptomatic conditions of a relatively simple character most of which can be managed on an ambulatory or home basis. I would include such things as upper respiratory infections most of the exanthems of childhood, providing a truss for a hernia medication for anxiety or a minor depression therapy for angina pectoris etc

It is here where the distinctions become somewhat blurred. Pneumonia if it is mild can be treated in the home or on an ambulatory basis but may require hospitalization and there may or may not be complications The same holds true for hernia hemorrhoids, prolapsed intervertebral disc and a host of other conditions.

Hospitalization should be needed only occasionally for treatment of a primary condition for example if one susp that the hypertension is not "essential" but has some spe unrecognized cause Diagnosis and treatment of second and tertiary conditions, however will frequently req in hospital management

A tertiary condition is one where a symptomatic disea complex and requires specialist expertise for example c nary bypass surgery for angina pectoris special treatment acute leukemia diagnosis and treatment for Hodgk disease etc Again the categories may become blurred some of these conditions are secondary rather than terti and some can be treated on an ambulatory basis, at l during certain stages of the disease

The desire to categorize and therefore make rules or le late can be understood but overdoing it will certainly lea injustice and difficulties for the patient and physician M physicians render primary secondary and tertiary car varying degrees for example Putting people into rigid bl boxes therefore is unjustified and should be discoura After all we are all human and therefore individual different although alike in some respects only

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Working status of patients following coronary bypass surgery

Coronary artery bypass grafting has become a common elective surgical procedure in most major medical centers in this country This operation has enabled more than 75 per cent of patients previously incapacitated by angina to obtain partial relief of symptoms or to become entirely free of pain in the first several years after operation Patients exercise longer with less pain within the year after operation, and as many as 68 per cent of patients demonstrate increased functional capacity The effects of operation on prolongation of life are less certain Controversies on the effectiveness of coronary bypass grafting in preventing myocardial necrosis and cardiovascular deaths flourish. Despite the unresolved issues concerning the effects of revascularization procedures the indisputable symptomatic improvement suggests th patients could be expected to return to work and lead mo productive lives after operation

Available reports on the return to work after the bypa operation however are disappointing. In a group of patients studied before and one year after coronary bypa grafting at the University of Alabama Medical Center the was no net improvement in return to work or hours work after operation. Of 132 patients not working or work part-time before surgery 7 per cent remained in that statu only 25 per cent resumed full time employment afterward The great majority of patients 218 were already worki full time prior to operation and 6? per cent of them continue

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to do so but the other 34 per cent decreased either to part time work (13 per cent) or to not working at all (21 per cent) Over all, 22 per cent of the patients decreased their hours worked classification 59 per cent stayed in the same classification and 19 per cent increased their work level. Rimm and co-workers[6] evaluated postoperative occupational status in 893 men with a median follow up time of 14 months after operation. They found 11 per cent of the younger men and 26 per cent of the older men employed before the operation retired following surgery while about one-fifth of the 9 per cent who were retired prior to operation came out of retirement Analysis of physical demands on the job revealed that 49 per cent of the patients took new less demanding jobs while only 40 per cent took jobs that were more demanding physically David and associates observed that 62 per cent of 500 men after operation were working and 38 per cent were inactive In the Seattle Heart Watch, 75 per cent of 1 098 patients had jobs three months before operation but only 62 per cent continued to work full time one year later When compared to a medically treated group adjusted for functional class education and age there was no indication that surgical therapy increased the likelihood of gainful employment in patients with coronary disease

Work status prior to surgery undoubtedly a function of motivation socioeconomic status, extent of disability and severity of disease appears to be the major predictor in determining return to work afterwards A period of invalidism of more than six months before operation results in a 50 per cent chance of permanent inactivity Many individuals do not go back to work or to more productive lives after coronary bypass surgery even though they are markedly improved in terms of symptoms and functional capacity Objective examination of the patients studied by David and co-workers revealed that 77.5 per cent of these patients were able to work. Logue and colleagues noted that only 50 per cent of patients returned to work, although 90 per cent had symptomatic improvement and relief of angina Physiologic improvement is sufficient to bring some patients back to work while others need additional motivation Other important considerations include the educational level of the patient severity of ischemic disease and the number of grafts placed. Age when adjusted for other factors appears to have little independent effect on subsequent employment Physical or mental demands of the job may have precluded some of the persons from working Kushnir and co workers demonstrated a differential rate of return to work following myocardial infarction between those patients who considered that work triggered their illness and those who did not. Unquestionably a number of patients capable of working do not wish to do so for various psychosocial and/or monetary reasons. Patients motivated to return to work for economic reasons did so yet those with attractive disability programs often retired.

To complicate the problem persons having a major surgical procedure enjoy undue attention from friends and family or other rewards from their inactivity Such persons have little incentive to resume productive activity The family and physician may reinforce such behavior by adopting an overly protective role for the patient An especially impressive finding in the Canadian study was that 60 6 per cent of patients attributed their non return to work to medical advice Physicians often play a counterproductive role by encouraging patients to isolate themselves from any work environment and certifying them as disabled despite exercise capabilities greatly exceeding any physical demands required on the job Employers are not always willing to accept former employees at high risk for work related injuries or illness. It should be apparent that recovery from coronary artery bypass surgery poses special problems for work rehabilitation

Currently indications for surgical therapy include relief of angina refractory to medical management and the probability of increased survival for selected subgroups. It is unlikely that there will be a curtailment of revascularization procedures in the immediate future but rather an escalation of costs The financial implications of coronary artery bypass surgery cannot be ignored Without consideration of indirect costs, the hospital charges and medical fees for more than 70 000 operations performed annually at an estimated cost of over $10 000 each approaches a billion dollars. Increased economic productivity for these individuals, mostly in middle age is not an unreasonable expectation for this enormous investment of resources. Effler believes our economy can not only accommodate the enormous cost of surgically managing patients with coronary disease but also can benefit as these patients go from invalidism to gainful activity This possibility exists as a primary justification for the operations, but has not yet materialized Short term results and available data do not demonstrate increased economic productivity after operation for these patients. If the maximum benefits of coronary artery bypass grafting are to be realized physicians caring for patients after surgery must take a more positive role in returning their patients to work

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What can we learn from the coronary bypass debate?

The coronary bypass operation is an unprecedentedly successful procedure True it is expensive highly publicized and this had led to its becoming inevitably controversial There is nothing wrong with controversy when the differences are honest and constructive but this debate has become polarized to a degree that can only work to the detriment of medical practice Well meaning individuals are advocating that this operation and all other expensive treatments be subjected to federal control in much the same way that the Food and Drug Administration controls medication This recommendation is an excessive reaction It implies not only that we are incapable as professionals of settling our own differences but that this control is required for retributive reasons as well It also implies that we can have no faith in our intuitive understanding which derives from clinical experience

There are several reasons why we must avoid a simplistic legalistic solution to the controversy

First medicine requires the freedom that allows for the innovations that lead to new treatments This is as true of medical treatment as it is of surgical procedures Second we have a system of checks and balances within the practice of medicine that are very effective in maintaining our professional responsibility for the patient s welfare Thirdly both the intuitive clinical approach and the objective scientific approach are valuable in the assessment of our results, but there are limitations to both and they must be understood

Innovation

Nowhere are the results of freedom which permits innovative treatment better illustrated than in the treatment of angina pectoris The use of propranolol for relief of ischemic pain was widely applied before it was officially recognized by the Food and Drug Administration for such use Coronary bypass also developed because the techniques for cardiopulmonary bypass and microsurgical procedures which were developed in another context were applied to overcome the circulatory defect that led to the pain of angina The medical treatment decrea the oxyg n requirement and the surgical procedure increases th oxygen supply

Application of these two procedures by their advocates rapidly led to agreement that many cases could be treated medically but that those which did not respond would be helped by surgery Neither the medical treatment nor the operation would have developed in a rigidly regulated system but surgery does seem more vulnerable because by its nature it must be done openly Operative therapy must evolve and the techniques must be refined. To presume that an operation can be tested in its initial stages is naive At present the coronary bypass operation has been improved to a point where it is no longer reasonable to judge it on the basis of the randomized studies completed to date It is critical that we rely on something other than simplistic science to test our therapies

Checks and balances

The checks and balances within the medical referral system are a critical factor which assumes that professional responsibility is met The adversary role of the cardiologist vis-a-vis the cardiac surgeon is an important example of this mechanism The relationship is somewhat out of hand when carried to the extremes of the current controversy but discounting the extremists on both sides it is clear that the cardiologist and the referring family physician play the important role in deciding whether or not surgery is to be considered Technical factors relating to operability are the surgeon s province but in a typical case the primary physician refers a patient with angina to a cardiologist for diagnostic studies when he has reached a medical impasse The cardiologist will then either refine the medical treatment thereby relieving symptoms or ask for consultation with a surgeon whose work he respects The surgeon will reevaluate the patient and review the coronary anatomy and cardiac performance recommending an op ration if he feels that it is technically feasible This progression assures that the patient receives optimal treatment for relief of his pain This system depends upon competent responsible individuals for its success If we don't have that then no amount of regulation will solve the problem

Science versus intuition

Finally we have to accept certain limitations which are inherent not only in our own personal evaluation of our experience with this operation but also in controlled randomization of medical versus surgical treatment

Intuition is cognitive knowledge something that we simply come to know by virtue of our experience When we say "Just give me the numbers we show our lack of trust in subjective knowledge But numbers lie too and blind faith in

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them is certainly an equal foolishness to the self seeking gut reaction

We know because the patients tell us that they are benefited by the coronary bypass operation For the most part when their grafts are open, they are free of pain They also know that when the grafts close the pain returns. Even more important when the occluded grafts are reoperated the pain is again relieved We don t have to see this too many times to begin to believe that there is a real benefit from the operation All we have to do is believe the patient trust our experience

On the other hand what rational person would believe the randomized studies which di prove the benefits of surgery? All except one are too deficient in numbers to be valid statistically and the largest one asks the wrong question by comparing medical treatment with operative results that do not compare with those which currently are acceptable regarding both mortality and graft patency rate

The best that can be said is that we need a valid study of the group to substantiate what we see in individuals The lessons of the coronary bypass debate are not that we have to impose an external control on our therapeutic innovations, not that we have failed ourselves scientifically and above all not that any one or another faction is culpable Rather the lessons are that clinical progress results from allowing reasonable creativity the control of such innovation is built into the referral practice of medicine by the adversary roles of the cardiologist and the cardiac surgeon and finally we must trust both our experience and our research but that neither is infallible

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Of senile cardiomyopathy

For some peculiar reason physicians seem to accept the fact that everything ages except the heart This attitude is difficult to understand Surely the heart and all of its parts must age Unfortunately the development of senile cardiomyopathy is difficult to establish by direct scientific observation because with aging coronary arteriosclerosis develops and it is impossible to delineate changes due to senescence itself and changes due to ischemia. Nevertheless no one will deny that all other things on earth age and certainly change with time Then why not the heart too? Furthermore no physician will deny that skeletal muscle ages. One needs only to see an 80 year old man attempt to high jump or pole vault or run a 100 meter dash to convince him that skeletal muscles age These efforts reveal the existence of senile skeletal myopathy The smooth muscle of a person s gastrointestinal tract ages So does his brain. And so must his heart and his myocardium

To accept as a fact that the myocardium ages and that senescence results in "senile cardiomyopathy would be good practice and would be especially rewarding in preventive cardiology " This practice is particularly important in advising patients concerning strenuous and uninterrupted exertion Not infrequently one hears about an aged acquaintance or an aged patient who died suddenly during continuous strenuous exercise or shortly after such exercise The same problem applies to an aged person who loses a portion of his myocardium from infarction and is left with less senile myocardium to carry on the work of the entire heart All of these situations may be viewed as driving the senile myocardium of an aged person in much the same manner as whipping a dying horse

Managing aged people as though they all have senile cardiomyopathy is a rewarding clinical experience for the physician and his old patient

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On "Of jogging"

To the Editor

Dr Burch's recent Annotation indicates that the American Automobile Association reported that 8 300 joggers were killed and over 100 000 were injured in 1977 by virtue of being hit by automobiles His reference is the March 22 1978 edition of the *Wall Street Journal* which indeed stated these figures on page 1 but with reference to the incidence of *pedestrian* deaths[1]

The American Automobile Association has informed me that in 1977 *total* pedestrian injuries (ages 0 to over 65 years) were estimated to be 100 000 and pedestrian deaths were 8 700 The breakdown of total deaths and injuries by circumstance is shown in Table I (Total 1977 traffic deaths including pedestrian deaths was 49 500)

Table I Total pedestrian deaths and injuries by category

Crossing or entering street or at intersection	69 242
Walking	8 261
Standing in roadway	4 131
Pushing or working on vehicle in roadway	2,283
Other labor in roadway	1 087
Playing in roadway	3 913
Other activities in roadway	11 957
Other activities not in roadway	7 826
Total	108 700

I am certain that the incidence of joggers killed by automobile is finite although it is not known Both driver and jogger I will allow are too frequently reckless when in a situation of confrontation prudence by both is in order Dr Burch's conclusion that jogging (is) a serious and dangerous disease of the environment strikes me as faulting the victim not the perpetrator Perhaps it is the automobile and its driver that should be considered the etiological agents of pedestrian deaths

Note added in proof Pedestrian deaths in the 1967 1977 period *declined* by 7% the jogging boom notwithstanding (see ref 3 page 58)

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Long term prognosis of bacterial endocarditis

To the Editor

I read with interest the paper by McNeill Strong and Lockwood on the long term prognosis of bacterial endocarditis in the April 1978 issue of AMERICAN HEART JOURNAL

Unfortunately there are inconsistencies between the numbers given in the table the figure and the text For example the number of patients surviving 1 year after multiple organism infection is three out of five in the table vs 100 per cent in Fig 1 For cases with sterile culture the numbers are four survivors out of 16 (25 per cent) in the table 31 per cent in Fig 1 and the discussion gives yet another number—28 per cent The text gives no explanation for these differences

Though the differences are slight they give the reader a feeling of doubt as to the reliability of the results of this interesting study

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REFERENCE

1 McNeill K M Strong J E Jr and Lockwood W R Bacterial endocarditis An analysis of factors affecting long term survival AM HEART J 95 448 1978

Reply

To the Editor

Dr Liron quite properly points out three discrepancies in our article (AM HEART J 95 448 1978) The correct figures as obtained from the original chart reviews are as follows Sterile cultures were found in 16 patients of whom five survived a year Multiple organisms were isolated from five patients all five of whom survived a year The other numbers as given in the table and the text are errors I overlooked while proofreading the typescript following a major revision

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Programmed atrial versus programmed His bundle stimulation

To the Editor

We have read with great interest the paper entitled Study of the temporal effects on conduction and refractoriness of the His Purkinje system in man by Dr Reddy and associates in the September 1978 issue of the JOURNAL This paper clearly demonstrated temporal stability of refractoriness in the His-Purkinje system Results of the study provide baseline data for future investigations of antiarrhythmic drugs acting on the distal part of the A V conduction system However in over 90 per cent of the cases investigated *programmed atrial stimulation* proved to be ineffective in assessing refractoriness of the His-Purkinje system because of A V nodal refractoriness

Theoretically *programmed His bundle stimulation* seems

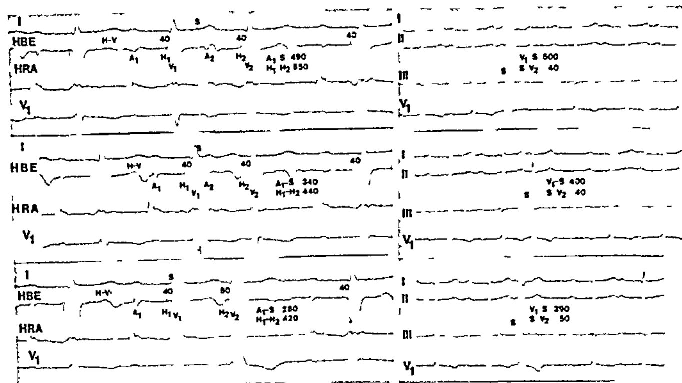


Fig 1 *The left and right panels* show atrial and His bundle extrastimulation with paper speeds of 100 and 50 mm/sec., respectively *Top* Extrastimuli with normal QRS complexes *Middle* The longest H H and V-S intervals associated with incomplete right bundle branch block (relative refractory period with aberration) *Bottom* The longest H H and V S intervals associated with complete right bundle branch block, H V, and S-V prolongation (relative refractory period with H V prolongation)

to be the ideal approach to delineate electrophysiological properties of the His-Purkinje system. As was demonstrated *in animal experiments* from the same laboratory our preliminary results *in man* also indicate that programmed His bundle stimulation is the most useful method in measuring refractoriness of the His Purkinje system We have found this method to be successful in the majority of cases in patients with intraventricular conduction disturbance An illustrative example for validation of this technique in evaluation of the His Purkinje system is presented in Fig 1 by comparing responses obtained during programmed atrial and His bundle stimulation

In the future programmed His bundle stimulation will probably allow more thorough categorization of the intraventricular conduction disturbances and a more accurate assessment of drug effects on the His-Purkinje system.

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3 Tenczer J., Littmann L., Molnár F., and Kékes, E. Electrophysiological studies in infra His conduction defects, *Fifth International Congress on Electrocardiology* Abstracts 1 10-5 1978

Reply

To the Editor

We thank Drs Littmann and Tenczer for their comments concerning our recent publication. We agree that in the majority of patients the determination of refractoriness of the His Purkinje system (HPS) by the atrial extrastimulus method is limited by the A V nodal refractoriness and programmed His bundle (HB) stimulation may be an ideal method for measuring the refractoriness of HPS However several theoretical and practical consideration may make this technique less valuable in clinical situations (1) stable HB pacing may be difficult to achieve in all patients because of anatomical variations and catheter movement caused by cardiac and respiratory movements[1] (2) the electrode catheter used for pacing the HB may pace several structures in the vicinity of HB—i.e., HB right bundle ventricular muscle resulting in variable QRS patterns and changing stimulus to ventricular activation (S-V) intervals (3) S-V interval may also vary depending upon the region of the HB paced (4) the higher stimulus strength required to pace the HB may affect the

propagation of impulses into the distal conducting system resulting in changes in refractory periods of HPS and (5) in patients with intra His bundle disease intra His conduction delay and block may be missed by HB pacing However the latter circumstance was not a limiting factor in the group of patients we studied

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5 Narula, O S., and Samet P Wenckebach and Mobitz type II A V block due to block within the His bundle and bundle branches Circulation 41 947 1970

Coronary heart disease—the doctor s dilemma

To the Editor

Regarding the above titled editorial of Dr George V Mann (AM HEART J 96 589 1978) besides the "doctor's dilemma" there is an additional "truth dilemma" concerning interpretation of bibliographic reference No 25 (Keys A Coronary heart disease in seven countries Circulation 41(Suppl. I) I 1 1970)

Dr Mann states " A most impressive collection of evidence suggests that exercise and fitness protect from CHD "As a co-author of the work referred above I would like to emphasize that no such statement regarding the protecting effect of exercise and fitness has been made in this monumental work. In not one of the seven countries has the incidence of CHD been influenced by occupation or physical activity on the job with the exception of the statistically non-significant trend for Dalmatia and Slavonia Still, for the Greek cohort on the island of Crete where the lowest incidence of CHD has been found for the past 20 years such a relationship has not been documented In the seven-country study other factors were of more importance and the results have opened new stimulating areas for research.

It is my opinion that little of value comes from speculations and that the doctor s dilemma" concerning CHD etiological relationships would be eased if bibliographic selection and interpretation were more objective

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Table G11 Frequency (f) of large Q waves (Code I, 1) in the electrocardiograms of men age 40-59 years by occupational physical activity class Rate is age adjusted rate per 1 000 men

Area	*Occupational physical activity class* Light f	Light Rate	Moderate f	Moderate Rate	Heavy f	Heavy Rate
U.S Railroad Men	13	12.9	13	18.3	–	–
East Finland	4	40.2	2	12 4	1	2.2
West Finland	2	29 8	4	33.3	0	0 0
Zutphen	5	19.8	4	8 0	0	0 0
Dalmatia	0	0 0	0	0 0	0	0 0
Slavonia	1	6 4	0	0 0	2	3 6
Montegiorgio	2	36 9	1	4 2	1	1 6
Crevalcore	2	17 0	0	0 0	3	3.9
Rome Railroad Men	1	10 4	1	2 7	2	9.5
Crete	0	0.0	0	0 0	1	2 4
Corfu	1	5.8	1	5 0	1	4.4
All areas combined	31	16.3	26	7 6	11	2.8

Average of the rates for all areas
(Reproduced from Acta Med. Scand Suppl. 460 1967 Reproduced by permission)

Reply

To the Editor

I believe the most appropriate response to the letter of Dr Aravanis is the reproduction of Table G11 from the publication of A Keys C Aravanis and others Epidemiological studies related to coronary heart disease Characteristics of men aged 40 59 in Seven Countries Act Med. Scand., Suppl. 460 1967 That work describes the characteristics of 11 000 men at the beginning of the Seven Nation Study For the benefit of Dr Aravanis and others who may not have seen the report in its entirety the authors comments are quoted here

"Table G11 and Figure G7 show the interesting diminution of "infarct" Q waves according to increasing activity of the occupation. Though the prevalence overall is low the difference is consistent within each age quinquennium as it is in the pooled data The frequency of large Q waves observed in the three activity classes (sedentary = 16.3/1000 moderate = 7 6/1000 active = 2.8/1000 differ significantly from each other ($p < 0.003$ in each case) "

Left axis deviation negative T waves and post-exercise S-T depression showed similar trends The first sentence of the authors discussion and conclusion is also interesting

"If large Q waves, so defined represent in fact a core of well established coronary cases (infarction) the relationship seen here between prevalence of coronary disease and activity habit is impressive

I try to minimize the reprint business but I would be glad to send Dr Aravanis this one of his own publications if that would encourage him to look at all the facts all the time

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Book reviews

Factors Influencing Vascular Reactivity Edited by Oliver Carrier Jr and Shoje Shibata Tokyo and New York 1977 Igaku Shoin Medical Publishers Inc

This book is an extremely important one for several reasons Most significant is the need to consider more seriously the functional state of the blood vessels that deliver the blood to the cells of the body Their physiologic function in health and disease must be considered in all patients not only those with overt vascular disease that brings them to a doctor but in all patients with, e g hypertension congestive heart failure arteriosclerosis, angina infarction thrombosis and embolism etc This book is on the fundamental aspects of vascular responses and includes 12 chapters concerned with the ultra structural basis for vascular smooth muscle reactivity biochemical aspects of vascular reactivity electrolytes drugs aging sex hormones and others There is a rather extensive selected bibliography appended to each chapter The illustrations are good and the many contributors present their concepts well This is a good book that should interest all doctors but especially physicians managing vascular disease physiologists and pharmacologists. This is a good addition to the medical literature

Atlas of Echocardiography By Ernesto E Salcedo Philadelphia, 1978 W B Saunders Company 236 pages Price $15 00

This is an excellent atlas on an important advancement in cardiac diagnosis As in other books on the subject the anatomy technical and theoretic considerations are discussed first These chapters are followed by discussion of the normal and abnormal echocardiographic manifestations. The numerous recordings presented are excellent and the legends are clearly written The text is brief and clearly related to the ECHO concept and the associated illustrations The labelling is good. This is extremely important since the book is essentially a compendium of echocardiograms This is one of the best books on echocardiography that this reviewer has encountered The book is well worth the price not only for those who are learning ECHO but also for those who regularly interpret the tracings.

Management of Essential Hypertension By F Gilbert McMahon M D Mount Kisco New York 1978 Futura Publishing Company 468 pages. Price $18 50

McMahon has produced an important and excellent book on the management of hypertension He reviews clearly and effectively the drugs now used in the management of high blood pressure one of the most important and still controllable diseases of man Each drug is discussed in detail with the practicing physician and its use in patients in mind. The drug is described its action and indications for use contraindications drug interaction side effects dosage and possible and potential beneficial effects are described clearly New drugs not yet approved by FDA for use are also discussed in the last chapter of the book This book should be owned by all doctors who treat hypertension. Undergraduate medical students housestaff and fellows in medicine will find this to be an extremely useful book McMahon has rendered a fine service to the field of medicine A very good book which has a well chosen bibliography appended to each chapter devoted to each drug is now available for clinicians.

Handbook of Experimental Pharmacology volume 39 Antihypertensive Agents Edited by Franz Gross, Berlin Heidelberg and New York, 1977 Springer Verlag 779 pages Price $128 80

This is an excellent authoritative review of the hypertensive agents written by 23 contributors from the fields of clinical medicine the pharmaceutical industry pharmacology and clinical pharmacology The 13 chapters review the antihypertensive drugs chemistry of these agents, the ganglion blocking drugs, rauwolfia alkaloids, adrenergic neuron blocking drugs, clonidine and related products, vasodilator drugs acting on the arteriolar smooth muscle diuretics, the renin-angiotensin system veratrum drugs and clinical pharmacology as well as other related agents The bibliographies are well selected the discussions and presentations are well organized and clear The illustrations are good and the texts are written without prejudice to any drug or drug combinations. This is an excellent book which is highly recommended for study and consideration in the management of hypertension

Books received

MGH Textbook of Emergency Medicine Edited by Earle W Wilkins Jr M D., Baltimore 1978 The Williams & Wilkins Company 829 pages. Price $49 50

Radiology Management of the Massively Traumatized Patient By Robert J Ayella M D Baltimore 1978 The Williams & Wilkins Company 297 pages. Price $40 00

Adolescent Medicine By I Ronald Shenker New York, 1978 Stratton Intercontinental Medical Book Corporation 376 pages. Price $35 00

The Jewish Low-Cholesterol Cookbook By Roberta Leviton Middlebury Vt., 19 8 Paul S Eriksson 370 pages. Price $14 95

propagation of impulses into the distal conducting system resulting in changes in refractory periods of HPS and (5) in patients with intra His bundle disease intra His conduction delay and block may be missed by HB pacing.[5] However the latter circumstance was not a limiting factor in the group of patients we studied[1]

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Coronary heart disease—the doctor s dilemma

To the Editor

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	Occupational physical activity class					
	Light		*Moderate*		*Heavy*	
Area	*f*	*Rate*	*f*	*Rate*	*f*	*Rate*
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East Finland	4	40 2	2	12 4	1	2.2
West Finland	2	29 8	4	33 3	0	0 0
Zutphen	5	19.8	4	8 0	0	0 0
Dalmatia	0	0 0	0	0 0	0	0 0
Slavonia	1	6 4	0	0 0	2	3 6
Montegiorgio	2	36 9	1	4 2	1	1 6
Crevalcore	2	17 0	0	0 0	3	3 9
Rome Railroad Men	1	10 4	1	2 7	2	9.5
Crete	0	0 0	0	0 0	1	2 4
Corfu	1	5 8	1	5 0	1	4 4
All areas combined	31	16.3	26	7 6	11	2.8

Average of the rates for all areas
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Reply

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American Heart Journal

August 1979 Volume 98 Number 2

Editorial

Cardiac auscultation a re-emphasis

Clues from physical maneuvers and pharmacologic agents

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Major advances in our understanding of the genesis of heart sounds and murmurs have taken place over the past several years Information gained from correlating the findings of cardiac auscultation phonocardiography cardiac catheterization and echocardiography has greatly improved our understanding of normal as well as pathologic cardiac acoustic events Translated into clinical practice this new information emphasizes the bedside evaluation of the patient as of major importance in the identification of cardiovascular disorder Unfortunately this fact has been not properly emphasized in the midst of our technologic explosion All too often one or more non invasive or even invasive cardiac diagnostic studies are undertaken without careful assessment of the physical findings Similarly the results of such diagnostic studies are not always interpreted in the context of the patient s signs and symptoms

What can we do to reap greater rewards from cardiac auscultation? First the teaching and reteaching of cardiac auscultation is critically important Teaching techniques have been improved markedly in the last several years with the development of high fidelity amplifiers as well as simultaneously displayed phonocardiographic traces Without such tools it is unlikely that the ever enlarging number of students and housestaff would acquire adequate training in cardiac auscultation Still there is no substitute for the one on one examination of the patient by the physician Quiet surroundings a comfortable patient and a comfortable physician with a good stethoscope are essential Too often these simple requirements are minimized and the outcome is unsatisfactory

Particularly helpful in the differentiation of innocent from pathologic heart sounds and murmurs has been attention to the response to changes in cardiac cycle length respiration physical maneuvers and vasoactive drugs

It has been more than one hundred years since Potain[1] called attention to the respiratory splitting of the second heart sound It was however not until 25 years ago that Leatham[2] brought this observation to clinical attention and emphasized its significance We have subsequently recognized the help that may be gained by attention to respiratory variation in other heart sounds and murmurs On inspiration the decrease in intrathoracic pressure that occurs results in an augmentation of right heart flow and a decrease in left heart flow Murmurs from within the right heart therefore generally increase while those originating from the left heart chambers decrease Thus on inspiration right ventricular S_3 and S_4 sounds are augmented as are the murmurs of tricuspid regurgitation tricuspid stenosis pulmonic stenosis and congenital pulmonic regurgitation Murmurs originating from the left heart are heard best in expiration when left heart filling is maximal and the amount of air filled

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lung interposed between the heart and the chest wall is least These changes are generally well heard with normal respiration Occasionally, the patient will need to be asked to breathe more deeply It is generally best to demonstrate to the patient the rapidity and depth of respiration desired In patients with pulmonary hypertension and marked right heart failure inspiratory increase in right heart murmurs and gallops may not occur because there is very little increase in right heart flow with inspiration in this setting Attention to the respiratory variation in acoustic events when the patient is standing (thus decreasing right heart filling pressure) may bring out the expected changes

A simple though often neglected, aspect of the cardiac auscultory examination is the assessment of the effect of postural change on heart murmurs The drop in systemic venous return that occurs going from a recumbent to sitting or standing position results in prompt physiologic changes and alteration of heart sounds and murmurs Stroke volume decreases with reflex increases in cardiac rate and systemic vascular resistance Listening as the patient goes from recumbent to sitting and/or standing position one notes a diminution in all murmurs from the right as well as the left heart except for those systolic murmurs of idiopathic hypertrophic subaortic stenosis (IHSS) and the mitral valve prolapse syndrome In IHSS standing causes the left ventricular outflow tract to be more obstructed due to the diminution of the left ventricular size as well as the reflex inotropic stimulus that results The patient with mitral valve prolapse syndrome similarly may have the systolic click and the murmur move earlier in systole in response to the smaller left ventricle that occurs on standing Additional information may be obtained by having the patient assume a squatting position The initial increase in venous return as well as increase in peripheral resistance that occurs with kinking the femoral arteries results in higher systemic pressure as well as reflex slowing of the heart rate The murmur of IHSS may diminish or actually disappear upon squatting Right heart systolic murmurs as well as the murmurs of mitral regurgitation and valvular aortic stenosis increase The higher systemic arterial pressure achieved with assuming the squatting position may bring out a faint murmur of aortic regurgitation that otherwise would be missed Left ventricular S_3 and S_4 sounds may be augmented or heard only under the stress of squatting

Hencke and associates[3] in 1960 called attention to the augmentation of the murmur of aortic stenosis following longer cardiac cycles and the importance of this finding in differentiating this murmur from that of mitral regurgitation In the compensatory beats following a premature ventricular contraction or in the longer cycle lengths of atrial fibrillation increase in ventricular filling volume and augmented ventricular contractility result in an increase in the intensity of murmurs due to left or right ventricular outflow tract obstruction Regurgitant murmurs from the atrioventricular valves however, do not change appreciably following longer cycle lengths

The use of the Valsalva maneuver may be helpful in differentiating right sided systolic murmurs from those originating in the left heart as well as in recognizing the murmur of IHSS It is generally necessary to demonstrate to the patient how to perform the Valsalva maneuver and to allow him to practice this maneuver before trying to make assessments about the behavior of cardiac acoustic events During an adequately performed held phase of the Valsalva systemic venous return is markedly reduced or stopped with a subsequent decrease in cardiac output systemic arterial pressure pulse pressure and reflex increase in heart rate During the straining phase almost all heart sounds and murmurs are decreased Upon release of the Valsalva murmurs from the right heart return to control level usually within one or two cardiac cycles whereas those originating in the left heart do not return to control intensity until five to ten cardiac cycles have occurred During the straining phase with the reduced cardiac output and smaller left ventricular chamber the murmur of IHSS characteristically increases in intensity

Isometric handgrip has also been a helpful maneuver Once again it is important to demonstrate to the patient how to perform this maneuver It is particularly important that the patient not combine isometric tension with the Valsalva maneuver as many patients are prone to attempt With isometric handgrip heart rate cardiac contractility cardiac output and arterial pressure increase while ventricular chamber size is not significantly altered Left ventricular S_3 and S_4 sounds are often augmented or brought

out by this maneuver The murmur of mitral regurgitation particularly of that due to papil lary muscle dysfunction is often augmented Similarly, the murmurs of aortic regurgitation and VSD may increase The murmurs of IHSS and valvular aortic stenosis as well as those from the right heart are generally unchanged or decreased Also the diastolic rumble of mitral stenosis is often increased with the increase in cardiac output that results from sustained hand grip

The bedside administration of amyl nitrite has long been an easy safe and helpful aid in cardiac auscultation When inhaled it produces prompt systemic vasodilatation with subsequent fall in systemic blood pressure and reflex increase in heart rate and cardiac output Because of its pronounced hypotensive effects it should be administered to patients while they are recum bent The hypotension occurs generally within 30 to 40 seconds and may be very transient with the reflex increase in cardiac output occurring 30 to 60 seconds later The auscultatory effects are those of increasing all systolic ejection murmurs except for that of Fallot s tetralogy Also increased are the diastolic murmurs of mitral stenosis and tricuspid stenosis The drop in systemic pressure decreases the murmurs of aortic regurgitation mitral regurgitation the Austin Flint rumble ventricular septal defect patent ductus arteriosis and systemic arteriove nous fistula Since the systolic murmur of tetral ogy of Fallot originates across the stenotic pulmo nary orifice amyl nitriate causes a reduction in this murmur as a result of the drop in systemic arterial pressure and thus the impedance to ejec tion of blood from the right ventricle into aorta and therefore less pulmonary blood flow It is worth noting that some patients with ventricular septal defect will have a paradoxic increase in the intensity of their systolic murmur in response to amyl nitrite This has been noted to occur in patients with large left to right shunts and pulmonary arterial pressures greater than 60 mm Hg Vogelpoel and colleagues have theorized that this is the result of the pulmonary vascular bed being more reactive than the systemic arterial bed in these patients with large flow pulmonary hypertensive VSDs The use of amyl nitrite has been most helpful in clarifying the differential diagnosis of murmurs due to left ventricular outflow tract obstruction (which increase follow ing amyl nitrite) from those of mitral regurgita tion (which decrease) the apical diastolic rumble of mitral stenosis (which increases) from the Austin Flint rumble (which decreases) ventricu lar septal defect (which decreases) from pulmonic stenosis (which increases) and acyanotic tetralo gy of Fallot (which decreases) from isolated valvular pulmonary stenosis (which increases)

Less commonly used have been vasopressor agents such as phenylephrine hydrochloride methoxamine and angiotensin The increase that results in systemic vascular resistance and reflex reduction in heart rate and cardiac output cause auscultatory changes opposite to those of amyl nitrite Vasopressors may be helpful in eliciting a murmur of aortic reguritation or mitral regurita tion and of increasing that due to ventricular septal defect and the Austin Flint rumble Also it may be of help in differentiating types of left ventricular outflow tract obstruction in that it may dramatically decrease intensity of the murmur of IHSS while having little or no effect upon the murmur due to fixed left ventricular outflow tract obstruction

In summary it is important to re emphasize the role of careful cardiac auscultation in cardiac diagnosis Simple essentials of auscultation need to be observed and stressed in our teaching and practice Attention to variation in cardiac acous tic events in response to physical maneuvers and pharmacologic agents may provide considerable diagnostic information at the bedside

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Clinical communications

Echocardiographic study on diastolic posterior wall movement and left ventricular filling by disease category

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It has been demostrated that several varieties of heart diseases have abnormalities of left ventricular function in both systole and diastole [1] [2]

Although many studies have focused on the left ventricular systolic function there have been fewer studies of the left ventricular diastolic function in man This is due in part to technical difficulties associated with the simultaneous and continuous measurement of left ventricular pressure and volume throughout diastole

The relationship between left ventricular pressure and volume is a sensitive method of evaluating left ventricular diastolic function [3] However angiography introduces a possible distortion of true cardiac function because of the intracardiac injection of contrast material and may be contraindicated in patients with acute cardiac disease or severe heart failure Echocardiography provides an important alternative method of evaluation

Recent studies by Pombo and associates and Feigenbaum and colleagues have shown that the left ventricular volume can be estimated by echocardiography by using the cube of the distance from the interventricular septum to the posterior wall Instantaneous changes in the left ventricular dimension and volume can be thus estimated throughout the cardiac cycle

The purpose of the present study is to evaluate the left ventricular diastolic function in various cardiac conditions by an analysis of left ventricular posterior wall motion and left ventricular chamber dimensions

Materials and methods

Eight clinical cardiac diseases were evaluated. They were ten patients with constrictive pericarditis eight patients with idiopathic congestive cardiomyopathy (CCM) nine patients with non obstructive hypertrophic cardiomyopathy (HCM) nine patients with valvular aortic stenosis (AS) 14 patients with aortic insufficiency (AI) 12 patients with mitral stenosis (MS) ten patients with mitral insufficiency (MI) and 99 patients with systemic hypertension (HT) The patients with hypertension were separated into two groups on the basis of the blood pressure Group I (HT[I]) blood pressure between 150/90 (mean 110) mm Hg and 179/99 (mean 126) mm Hg Group II (HT[II]) blood pressure greater than 180/100 (mean 127) mm Hg The diagnosis in each patient was established by clinical evaluation non invasive studies and cardiac catheterization All patients were symptomatic except the patients with hypertension who did not have heart failure Seventy one patients were male and 44 patients were female aged 39 to 79 years (mean 63 years) All patients were in sinus rhythm with a heart rate between 50 and 90 beats per minute Twenty normal subjects without cardiac disease were used as controls

Mitral valve septal and posterior wall echocardiograms were recorded simultaneously with electrocardiography and phonocardiography using a method which has been previously described All recordings were made using the

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$$EDV = EDD^3, \quad ESV = ESD^3 \quad SV = EDV - ESV$$

$$EF = SV/EDV \quad RFV = RFD^3 - ESV$$

$$SFV = SFD^3 - RFD^3 \quad AFV = EDV - SFD^3$$

$$PWE = R + S + A$$

$$DPWV = R/e\ f \quad RFR = RFV/e\ f$$

Fig 1 Echocardiogram of the left ventricle and mitral valve and a schematic diagram illustrating the method of measurements *MV* = Mitral valve *IVS* = interventricular septum PW = left ventricular posterior wall *EDD* = LV end-diastolic dimension *ESD* = LV end systolic dimension RFD = LV dimension at the end of rapid filling period *SFD* = LV dimension at the end of slow filling period *PW Th* = thickness of posterior wall *R* = posterior wall excursion during rapid filling period *S* = posterior wall excursion during slow filling period *A* = posterior wall excursion during atrial contraction period *DPWV* = posterior wall velocity during rapid filling period *RFR* = rapid filling rate *DDR* = diastolic descent rate of mitral valve Ao A B C D E F and a b c d e f are defined as shown in the mitral valve and posterior wall echogram

ALOKA SSD 33 and 80 instruments with a repetition rate of 1 000 impulses per second and a 2 25 MHz unfocused transducer of 10 mm diameter The probe was usually placed in the fourth intercostal space just lateral to the left sternal margin The beam direction for the standard recording of the interventricular septum and posterior wall was just below the free edge of the mitral valve To obtain data from these echograms we divided the diastolic period into three phases—rapid filling period (early diastolic phase) slow filling period (mid diastolic phase) and atrial filling period (late diastolic phase) As shown in Fig 1 the timing of these phases was determined using the D Ao e f and a points in the mitral valve septal and posterior wall echograms The rapid filling period is defined as the time from D or e point to f point The slow filling period is from f to Ao or a point The atrial filling period is from Ao or a point to peak of R wa

Table I Posterior wall excursion (PWE) during three phases of diastole in 95 patients with various cardiac conditions and in 20 normal subjects

	Normal *n* = 20	*Pericarditis* *n* = 10	*CCM* *n* = 8	*HCM* *n* = 9
PWE (cm)	1 28 ± 0 23	0 98 ± 0 21 ↓	0 96 ± 0 27 ↓	1 47 ± 0 12
R (cm)	0 96 ± 0 18	0 73 ± 0 19 ↓	0 67 ± 0 20 ↓	0 76 ± 0 14 ↓
S (cm)	0 13 ± 0 07	0 05 ± 0 15 ↓	0 14 ± 0 12	0 36 ± 0 16 ↑
A (cm)	0 18 ± 0 10	0 21 ± 0 08	0 26 ± 0 29	0 35 ± 0 20 ↑
R/PWE	0 77 ± 0 06	0 73 ± 0 08	0 67 ± 0 09	0 54 ± 0 11 ↓
S/PWE	0 11 ± 0 05	0 05 ± 0 05 ↓	0 10 ± 0 09	0 24 ± 0 06 ↑
A/PWE	0 13 ± 0 06	0 22 ± 0 08 ↑	0 22 ± 0 11 ↑	0 22 ± 0 06 ↑

All abbreviations as in legends to Figs 1 and 2
All values are expressed as mean ± S D
Statistically significant difference ($p < 0.05$) between normal subjects and patients with various cardiac conditions
↑ increase
↓ decrease

Table II LV filling volume during three phases of diastole in 95 patients with various cardiac conditions and in 20 normal subjects

	Normal *n* = 20	*Pericarditis* *n* = 10	*CCM* *n* = 8	*HCM* *n* = 9
SV (ml)	95 ± 26	59 ± 35 ↓	97 ± 23	83 ± 28
RFV (ml)	61 ± 16	39 ± 28 ↓	58 ± 14	36 ± 19 ↓
SFV (ml)	17 ± 8	4 ± 5 ↓	14 ± 13	20 ± 7
AFV (ml)	18 ± 12	20 ± 13	26 ± 15	28 ± 11 ↑
RFV/SV	0 64 ± 0 10	0 65 ± 0 12	0 58 ± 0 13	0 41 ± 0 12 ↓
SFV/SV	0 17 ± 0 07	0 07 ± 0 08 ↓	0 14 ± 0 15	0 24 ± 0 06 ↑
AFV/SV	0 19 ± 0 09	0 28 ± 0 14 ↑	0 28 ± 0 15	0 34 ± 0 09 ↑

All abbreviations as in legends to Figs 1 and 2
All values are expressed as mean ± S D
Statistically significant difference ($p < 0.05$) between normal subjects and patients with various cardiac conditions
↑ increase
↓ decrease

b point as illustrated in Fig 1 LV wall and cavity dynamics were analyzed as follows

The amplitude of the posterior wall excursion was measured during rapid filling period slow filling period and atrial filling period (R S A respectively) (Fig 1) The fractional changes in the amplitude of the posterior wall excursion during three phases of diastole were obtained as the ratios of each of these to total posterior wall excursion (PWE) Using the method of Pombo and associates the left ventricular filling volume during each of these phases was obtained by cubing the distance from the interventricular septum to the posterior wall (at each period) The left ventricular filling volume during rapid filling period slow filling period and atrial filling period (RFV SFV AFV respectively) were calculated as shown in Fig 1 Filling fractions of the stroke volume (SV) during each of three phases of diastole were calculated as the ratios of RF' SFV and AFV to SV The mean velocity of th posterior wall (DPWV) and the rate (velocity) LV filling during rapid filling period (RFR) we also measured and calculated RFR was correcte by end systolic volume (RFR/ESV) The thicl ness of the left ventricular posterior wall (P Th) and ejection fraction (EF) were measure and calculated using the standard method F slope was measured in the mitral valve echogra and was compared with DPWV and RFR/ESV

All measurements were performed by magnify ing echocardiograms using a film motion analyze (NAC Model 35c) An analysis of variance wa used for statistical analysis

Results

1 Posterior wall movement (Table I) Th amplitude of the total diastolic posterior wal

AS *n* = 9	*MS* *n* = 12	*HT (I)* *n* = 10	*HT (II)* *n* = 13	*AI* *n* = 14	*MI* *n* = 10
1.13 ± 0.21	1.11 ± 0.23	1.26 ± 0.45	1.19 ± 0.23	1.38 ± 0.36	1.57 ± 0.44 ↑
0.57 ± 0.17 ↓	0.64 ± 0.13 ↓	0.8[illegible] ± 0.34	0.75 ± 0.[illegible]6 ↓	0.81 ± 0.31	1.22 ± 0.33 ↑
0.30 ± 0.14 ↑	0.35 ± 0.13 ↑	0.16 ± 0.13	0.19 ± 0.13	0.26 ± 0.09 ↑	0.15 ± 0.10
0.26 ± 0.11 ↑	0.13 ± 0.08	0.28 ± 0.1[illegible] ↑	0.[illegible]6 ± 0.13 ↑	0.3[illegible] ± 0.10 ↑	0.20 ± 0.08
0.49 ± 0.08 ↓	0.56 ± 0.1[illegible] ↓	0.66 ± 0.11 ↓	0.62 ± 0.16 ↓	0.56 ± 0.12 ↓	0.78 ± 0.05
0.27 ± 0.11 ↑	0.31 ± 0.08 ↑	0.12 ± 0.07	0.16 ± 0.12	0.19 ± 0.07 ↑	0.09 ± 0.06
0.24 ± 0.11 ↑	0.13 ± 0.06	0.22 ± 0.09 ↑	0.22 ± 0.1[illegible] ↑	0.24 ± 0.11 ↑	0.13 ± 0.05

AS *n* = 9	*MS* *n* = 12	*HT (I)* *n* = 10	*HT (II)* *n* = 13	*AI* *n* = 14	*MI* *n* = 10
85 ± 28	71 ± 30 ↓	114 ± 51	91 ± 3[illegible]	164 ± 82 ↑	144 ± 40 ↑
38 ± 16 ↓	2[illegible] ± 11 ↓	61 ± 2[illegible]	45 ± 2[illegible] ↓	[illegible] ± 48	92 ± 40 ↑
25 ± 13 ↑	3[illegible] ± 16 ↑	28 ± 19 ↑	19 ± 14	44 ± 29 ↑	[illegible]5 ± 13
22 ± 10	11 ± 5	28 ± [illegible]	[illegible] ± 16 ↑	43 ± 27 ↑	[illegible] ± 10
0.46 ± 0.08 ↓	0.37 ± 0.07 ↓	0.48 ± 0.18 ↓	0.49 ± 0.1[illegible] ↓	0.4[illegible] ± 0.16 ↓	0.[illegible]2 ± 0.12
0.30 ± 0.14 ↑	0.4[illegible] ± 0.07 ↑	0.[illegible]4 ± 0.12	0.[illegible]0 ± 0.1[illegible]	0.28 ± 0.1[illegible] ↑	0.18 ± 0.09
0.[illegible]6 ± 0.07 ↑	0.16 ± 0.04	0.22 ± 0.09	0.31 ± 0.17 ↑	0.2[illegible] ± 0.11	0.20 ± 0.09

excursion (PWE) was significantly decreased in patients with constrictive pericarditis and CCM In contrast it was increased in patients with MI The amplitude of the posterior wall excursion during the rapid filling period (R) was decreased while that during atrial contraction period (A) was increased in most patients (Table I) In addition to these changes patients with AS and HCM showed an increase in the posterior wall excursion during the slow filling period (S) while patients with constrictive pericarditis showed a decrease in both of R and S with a slight increase in A

Patterns of fractional changes in the amplitudes of the posterior wall excursion during three phases of diastole (R/PWE S/PWE A/PWE) paralleled patterns of changes in the amplitudes (R S A) in most patients However there were some exceptions R/PWE was normal despite a significant decrease in R in patients with constrictive pericarditis Patients with HT(I) HT(II) and AI showed a decrease in R/PWE with a significant increase in A/PWE while R and or A remained within normal limits

2 Pattern of left ventricular filling (Table II) Total left ventricular filling volume during diastole (=SV) was significantly decreased in patients with constrictive pericarditis and MS and increased in patients with MI and AI The left ventricular filling volume during the rapid filling period (RFV) was decreased and the atrial filling volume (AFV) was slightly increased in patients with HCM HT (II) and AS In addition to these changes in RFV and AFV the left ventricular filling volume during the slow filling period (SFV) was also increased in patients with AS RFV increased in patients with MI Decrease in both RFV and SFV was observed in patients with constrictive pericarditis RFV decreased with an increase in SFV and without significant changes in AFV in patients with MS Changes in the filling fractions of SV (RFV/SV SFV/SV

Table III DPWV RFR/ESV and DDR in 20 normal subjects and in 95 patients with various cardiac conditions

	Normal *n* = 20	*Pericarditis* *n* = 10	*CCM* *n* = 8	*HCM* *n* = 9
DPWV (cm/sec)	7.3 ± 1.8	5.5 ± 1.1 ↓	4.4 ± 1.1 ↓	4.3 ± 1.0 ↓
RFR/ESV	11.7 ± 4.4	8.0 ± 4.3 ↓	3.4 ± 1.4 ↓	5.2 ± 3.5 ↓
E F slope (mm/sec)	89 ± 19	82 ± 22	58 ± 10	33 ± 24 ↓

All abbreviations as in legends to Figs 1 and 2
All values are expressed as mean ± S D
Statistically significant difference ($p < 0.05$) between normal subjects and patients with various cardiac conditions
↑ increase
↓ decrease

Table IV EDD PW Th and EF in 20 normal subjects and in 95 patients with various cardiac conditions

	Normal *n* = 20	*Pedicarditis* *n* = 10	*CCM* *n* = 8	*HCM* *n* = 9
EDD (mm)	49 ± 3	44 ± 10	71 ± 6 ↑	48 ± 7
PW Th (mm)	9 ± 2	8 ± 2	10 ± 3	16 ± 2 ↑
EF	0.81 ± 0.09	0.69 ± 0.11	0.27 ± 0.10 ↓	0.75 ± 0.10

All abbreviations as in legends to Figs 1 and 2
All values are expressed as mean ± S D
Statistically significant difference ($p < 0.05$) between normal subjects and patients with various cardiac conditions
↑ increase
↓ decrease

AFV/SV) almost paralleled changes in the left ventricular filling volume during three phases of diastole (RFV SFV AFV) in patients with CCM HCM AS MS and HT (II) However patients with constrictive pericarditis HT(I) AI and MI demonstrated different changes Namely AFV/SV increased although AFV was normal in constrictive pericarditis HT(I) and AI showed significant decrease in RFV/SV despite normal RFV RFV/SV and AFV/SV remained within normal limits though RFV increased in patients with MI

3 Diastolic posterior wall velocity and rate (velocity) of LV filling during rapid filling period (Table III) As shown in Table III DPWV decreased significantly in most patients who also showed a decrease in R and R/PWE The mean rate of left ventricular filling during rapid filling period (RFR/ESV) was also decreased in patients who showed a decrease in the left ventricular filling volume during rapid filling period (RFV) This was observed in constrictive pericarditis COCM HCM AS MS HT(I II) and AI

4 LV dimension wall thickness and ejection fraction (Table IV) The left ventricular end diastolic dimension (EDD) was increased significantly in patients with CCM HT(I) AI and MI Among them CCM had the largest mean values of EDD The mean values of the thickness of the left ventricular posterior wall (PW Th) was increased significantly in patients with HCM AS HT(II) and AI among whom HCM showed the largest mean value of PW Th EF was within normal limits in almost all patients except CCM who showed a significant decrease

5 E F slope of anterior mitral valve (Table III Figs 2 and 3) E F slope decreased significantly in patients with HCM AS MS and HT(II) Among them MS AS and HCM showed a particularly prominent decrease E F slope was correlated well with DPWV ($r = 0.67$ $p < 0.01$) and RFR/ESV ($r = 0.56$ $p < 0.01$) However E F slope in patients with MS decreased to disproportionate degree with a decrease in DPWV and RFR/ESV

Discussion

Left ventricular diastolic abnormalities of various types and degrees of severity were revealed in almost all patients in this study by analyzing patterns of the left ventricular filling and diastolic posterior wall movements during three phases

	AS n = 9	MS n = 12	HT (I) n = 10	HT (II) n = 13	AI n = 14	MI n = 10
	38 ± 11 ↓	41 ± 09 ↓	56 ± 22	43 ± 13 ↓	53 ± 20 ↓	71 ± 14
	58 ± 16 ↓	57 ± 25 ↓	72 ± 39 ↓	63 ± 32 ↓	67 ± 25 ↓	15.5 ± 62 ↑
	30 ± 12 ↓	10 ± 5 ↓	79 ± 20	63 ± 20 ↓	62 ± 53	104 ± 33

	AS n = 9	MS n = 9	HT (I) n = 12	HT (II) n = 13	AI n = 14	MI n = 10
	49 ± 7	46 ± 6	53 ± 5 ↑	51 ± 8	62 ± 11 ↑	56 ± 6 ↑
	14 ± 3 ↑	9 ± 3	11 ± 3	13 ± 2 ↑	13 ± 3 ↑	11 ± 2
	0 72 ± 0 12	0 73 ± 0 09	0 77 ± 0 11	0 68 ± 0 10	0 67 ± 0 10	0 77 ± 0 07

of diastole and comparing the results with normals Disturbances in the left ventricular filling and posterior wall distension during the rapid filling period were observed in almost all patients except in those with MI The causes of the abnormalities are probably multiple These include thickening of the pericardium in constrictive pericarditis decreased left ventricular compliance and cardiac output in CCM myocardial hypertrophy and ischemia in AS and HT[1] and narrowing of the mitral valve ostium in MS In patients with AI LV filling volume during the rapid filling period remained within normal limits while rapid filling fraction of SV showed a slight decrease The reason for this discrepancy is unknown It is possible that the net effects of LV volume overload and a decrease in the left ventricular compliance will determine the diastolic properties of the left ventricle in patients with AI MI showed an increased LV filling *during the rapid filling* period This is probably due to the large volume of blood flowing into a compliant left ventricle[13] contrasting with MS This observation is of value in the differentiation between MS and MI

A decrease in left ventricular filling during the rapid filling period was often associated with an increase in atrial filling This augmented atrial contribution to the left ventricular filling probably represents a compensatory mechanism to maintain diastolic filling of the heart

Patients with constrictive pericarditis showed decreased distension of the left ventricular wall during the slow filling period (diastasis) This is analogous to the dip and the plateau of the left ventricular pressure curve This is probably due to the restriction of left ventricular distension by thickened pericardium

In patients with MS left ventricular filling during the atrial contraction period was not increased despite a prominent A wave in the left ventricular pressure recording This is probably due to the fact that the mitral orifice is too narrow for the augmented atrial contraction to make a significantly increased inflow of blood from the left atrium into the left ventricle

Patients with decreased left ventricular filling and distension of the left ventricular wall during the rapid filling period also demonstrated a decreased velocity of left ventricular filling and a distension of the posterior wall during the rapid filling period Patients with MS and marked left ventricular hypertrophy (AS HCM) had the slowest filling rate and sometimes there was no longer a true rapid filling phase because filling continued at a slow rate throughout diastole There have been several reports concerning the rate of LV filling [2] Lipchik and colleagues[11]

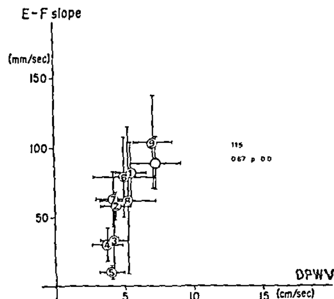


Fig 2 Relationship between DDR (diastolic descent rate of mitral valve) and DPWV (posterior wall velocity during rapid filling period) in 95 patients with various cardiac conditions and in 20 normal subjects The numbered circles with solid bars designate mean values and one standard deviation in patients with various heart diseases as follows ① constrictive pericarditis ② = congestive cardiomyopathy (CCM) ③ = hypertrophic cardiomyopathy (HCM) ④ = aortic stenosis (AS) ⑤ = mitral stenosis (MS) ⑥ = hypertension (HT(I)) Group I ⑦ = hypertension (HT(II)) Group II ⑧ = aortic insufficiency (AI) ⑨ = mitral insufficiency (MI) ○ Normal controls All abbreviations as in *Fig 1* A significant positive correlation ($r = 0.67$ $p < 0.01$) was found between DDR and DPWV

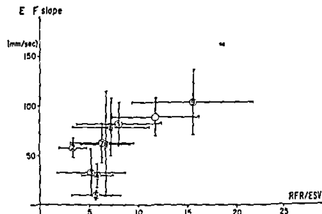


Fig 3 Relationship between DDR (Diastolic descent rate of mitral valve) and RFR/ESV (Rapid filling rate—end systolic volume ratio) in 95 patients with various cardiac conditions and in 20 normal subjects All abbreviations as in *Figs 1* and *2* A significant positive correlation ($r = 0.56$ $p < 0.01$) was found between DDR and RFR/ESV

measured inflow velocity of contrast material in angiocardiogram and showed that the maximum inflow velocity correlated well with left ventricular compliance stroke volume and ejection fraction Porter and associates and Hammermeister and Warbasse showed that maximum inflow velocity obtained by an analysis of left ventricular angiographic volume curves was decreased in patients with myocardial damage AS and MS Gibson and co workers[16] showed that the peak rate of increase of LV dimension and volume was greatly increased in patients with MI and reduced in patients with MS These observations are in agreement with the present study Fogelman and associates reported that the posterior wall velocity was decreased during anginal attacks This is probably due to a decrease in the left ventricular compliance or impaired myocardial relaxation caused by myocardial ischemia More recently Sutton and colleagues showed that there was an increase in the duration of the rapid filling phase with reduction in the left ventricular filling rate in HCM Factors which might determine the velocity of LV filling and LV wall distension during the rapid filling period are probably multiple and include a reduced myocardial compliance abnormal myocardial relaxation poor LV pump function and a reduced mitral valve orifice area

Analysis of diastolic posterior wall motion appears to reflect the sequence of LV filling fairly accurately Discrepancies occur largely when LV volume is increased Several studies correlating LV volumes derived from echocardiography with those from angiography indicated a good correlation but a large error especially when LV is enlarged The pattern of the posterior wall echogram during diastole is characteristic of the respective heart disease and thus may reflect various types of diastolic abnormalities The disease categories in the present study include a wide range of chronicity and severity and the diastolic behavior would reflect those variations sometimes more powerfully than the basic condition

Laniado and colleagues[1] compared echocardiographically recorded mitral valve motion with phasic trans mitral flow in 17 open chested dogs and showed that the mitral valve echogram mirrors the trans mitral flow pattern This finding suggests that mitral inflow velocity during rapid filling period is one of the determinants of the E F slope Actually our study demonstrated that E F slope correlated well with DPWV and

RFR/ESV which might reflect the mitral inflow velocity E F slope decreased in CCM HCM AS HT and MS In these diseases DPWV and RFR decreased due to a decrease in the left ventricular distensibility and cardiac output or narrowing of the mitral valve orifice which might result in decreased mitral inflow velocity and thus decreased E F slope In MS E F slope decreased much more than expected according to decreases in DPWV and RFR which may be caused by the decreased mobility of the mitral valve leaflet due to organic changes

In spite of these diastolic abnormalities of LV function the ejection fraction was normal in almost all patients except in those with CCM This indicates that the usual indices of systolic pump function are insensitive to diagnose diastolic abnormalities

The left ventricular filling pattern and the posterior wall motion during each of three diastolic phases assessed by echocardiography reflects well the types and severities of impaired diastolic hemodynamics of the left ventricle We conclude that the septal and posterior wall echogram offers a simple and non invasive means of assessing left ventricular diastolic function

Summary

The diastolic characteristics of the left ventricle with special reference to the patterns of left ventricular filling and diastolic posterior wall movement were studied echocardiographically in 95 patients with various cardiac conditions including constrictive pericarditis idiopathic cardiomyopathy (CCM HCM) valvular aortic stenosis (AS) mitral stenosis (MS) hypertension (HT) aortic insufficiency (AI) mitral insufficiency (MI) and in 20 normal subjects

1 Various types and severities of LV diastolic abnormalities were revealed by analyzing the patterns of posterior wall movement and LV filling in three diastolic phases—rapid filling period slow filling period and atrial filling period respectively

2 Disturbances of posterior wall distension and LV filling during the rapid filling period with a compensatory augmentation of atrial contribution to LV filling were observed in most patients These patients also showed a markedly decreased posterior wall velocity and LV filling rate during rapid filling period

3 E F slope was significantly decreased in patients with MS AS and HCM E F slope correlated well with DPWV and RFR in most patients In MS however DDR decreased to a disproportionate degree with a decrease in DPWV and RFR probably due to the structural changes and decreased mobility of the mitral valve

From this study we conclude that the patterns of the left ventricular filling and posterior wall movement during three phases of diastole obtained by echocardiography is useful in detecting left ventricular diastolic abnormalities

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HL-A antigens in Takayasu's disease

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Takayasu's disease is a form of vasculitis with the characteristic feature of pulselessness.[1-3] The aortic arch and/or abdominal aorta and main branches stenose and the blood flow is obstructed. Epidemiologic studies done in Japan[1] in 1975 revealed that 2,148 patients were suffering from Takayasu's disease and that 89 per cent of all patients were females. Takayasu's disease most often occurs in Asian or South American countries with very few incidences in Western countries.[2, 3] Even those cases reported from Western countries involve those with Asian origins. The pathogenesis of this disease remains obscure.

Recently, we encountered twin Japanese sisters both of whom were diagnosed as having Takayasu's disease.[5] The family histories revealed the parents to be first cousins. A causative factor which would induce this morbid condition could not be found in either twin.

The other three siblings, one boy and two other elder sisters, are quite healthy and these five children were born after a normal gestation and delivery. Moreover, all five children were reared in the same countryside in Japan. This background material led to the postulation of the participation of genetic factors in the cause of the disease and we investigated HL-A typings in these patients. Our data obtained are presented herein.

Materials and methods

Family study. As shown in Table I, 10 cases including our case of twin sisters have been reported in Japan as family cases of Takayasu's disease.[1] The parents in three families were first cousins. HL-A typings of all family members were studied in six families. Five ml. of venous blood samples were taken, heparin was added, and HL-A typings were studied with the lymphocyte microcytotoxicity test devised by Terasaki and McClelland and which involves complement-dependent lysis of lymphocytes by antibody. As shown in Table II, 10 in A locus and 15 in B locus of HL-A were studied using totally 96 types of anti-HL-A sera which were obtained from N.I.H. (U.S.A.) or were sera from Japanese pregnant women.

Population study. HL-A typings of 65 patients with Takayasu's disease were studied with the lymphocyte microcytotoxicity test method and were compared with those of 128 healthy Japanese. A statistical analysis was performed using χ test of antigens in association with this disease. This revealed a high frequency in the group of Takayasu's disease victims.

Results

Family study. Fig. 1 shows the genotypes of HL-A antigens in the Case I family. Both the mother, 64 years old, and her daughter, 36 years old, are suffering from Takayasu's disease. These clinical courses were reported by Taguchi and colleagues[1] in 1972. Both father and son are quite healthy and HL-A typings revealed that both

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Table I Family incidence of Takayasu s disease

Case No	Patients	Reporter	Area	Literature
1	Mother & daughter	Taguchi	Shizuoka	J Jap Soc Int Med 61 67 1972
2	Mother & daughter	Fukaya	Tochigi	Shindan to Chiryo 45 1900 19 0
3	Mother & daughter	Togawa	Ibaraki	
4	Two sisters	Koide	Tokyo	J Jap Coll Angiol 13 480 1973
5	Two sisters	Goto	Tokyo	Jap Circul J 26 947 1962
6	Two sisters	Kadota	Hyogo	Jap Circul J 40 151 1976
7	Twin sisters	Numano	Chiba	Circulation 58 173 1978
8	Brother & sister	Fukazawa	Gumma	Blood & Vessel 3 869 1972
9	Brother & sister	Yamaguchi	Mie	
10	Aunt & niece	Sato	Tokyo	

= HL-A typing was studied

Table II HL A antigen studied in Takayasu s disease and the number of antisera used for their determination

A locus		B locus	
HL-A antigen	No of antisera	HL A antigen	No of antisera
A 1	3	B 5	6
A 2	4	B 7	4
A 3	3	B 8	4
A 9	4	B 12	3
A 10	5	B 13	3
A 11	5	B 14	3
A 28	1	B 18	1
A 29	2	B 27	3
AW19	5	BW15	3
AW33	2	BW16	3
		BW17	3
		BW22	8
		BW35	3
		BW40	8
		BW54	7

children hold the same haplotypes of HL A antigens Fig 2 shows the genotype of HL A in Case II Here both the mother and daughter are victims of Takayasu s disease The parents are first cousins and the father and son are healthy A common haplotype of HL A A9 B5 was found in both mother and daughter In both Case I and Case II onset was at about the same age in the daughters while onset in the mothers is unknown

The third case is of a mother and one of two daughters suffering from Takavasu s disease Another sister is quite well The father died of apoplexy As shown in Fig 3 a haplotype of HL-A

Table III Disease associated haplotype and Takayasu s disease

Takayasu s disease / Disease associated haplotype	No of family members with	No of family members without	Total
Observed data			
(+)	11	8	19
(−)	0	11	11
Total	11	19	30
Corrected data			
(+)	5	8	13
(−)	0	11	11
Total	5	19	24

$\chi^2 = 7.8$ (Yate s formula)
$0.01 < p < 0.05$

AW33 BW40 was found in both the mother and daughter with Takayasu s disease

Fig 4 shows the HL A genotypes of our case of twin sisters (Case VII) and the related clinical studies have already been reported in detail[5] Ages at the time of diagnosis were 11 and 13 years respectively A haplotype of HL A A11 BW40 in the father passed to the twin sisters and not to the other children

Case VIII one brother and one sister have Takayasu s disease Eight other siblings are quite healthy and one brother and sister died in childhood Their father died of apoplexy The mother is 68 years old and enjoys a healthy life The sister detected her own pulseless condition in her right arm at 18 years of age and died of congestive heart failure at age 24 Fig 5 shows HL A typings

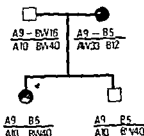


Fig 1 HL-A genotypes of family members in Case I ● = patients with Takayasu s disease = common haplotype was found in patients. Same symbols are used for all illustrations.

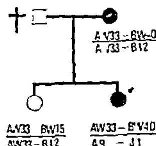


Fig 3 HL-A genotypes of family members in Case III

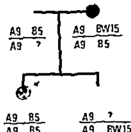


Fig 2 HL-A genotypes of family members in Case II

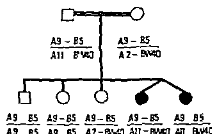


Fig 4 HL-A genotypes of family members in Case VII

of their mother and seven brothers and sisters Due to the death of the father and one sister with Takayasu s disease a haplotype associated with the disease could not be definitely determined

In Case IX among four children one brother and one sister have Takayasu s disease The oldest sister underwent aortic valve repair for a severe aortic insufficiency An artificial graft was made to replace a dilated aortic arch in the brother All showed the same HL-A phenotypes but due to the death of one parent the haplotype could not be determined (Fig 6)

Table III shows the correlation between Takayasu s disease and the disease associated haplotype in these six families In Cases V and VI possible haplotypes associated with the disease were assumed and calculated The upper part of the table shows the family members of healthy persons or those with Takayasu s disease with or without a disease associated haplotype In the corrected data in the lower part of the table the correlation was studied using Yate s formula in an attempt to detect a possible cause of disease associated haplotype with the level of 7 8 in the χ test (0 01 $< p <$ 0 05)

Population study Table IV shows the phenotypes in patients with Takayasu s disease HL-A A9 A10 B5 and BW40 exhibited a high frequency in patients with Takayasu s disease and statistical analysis certified a significantly high frequency of HL-A A10 ($p < 10^{-4}$) and B5 ($p < 10$) in Takayasu s disease victims as compared with those in normal Japanese (Table V) Values of the χ^2 test are 15 3 (A10) and 17 0 (B5) respectively [11] It should also be pointed out that there is a rare frequency of BW35 in Takayasu's disease as compared with the incidence in healthy Japanese

Discussion

Since the first description by Takayasu and Ohnishi[1] in 1908 the etiology of Takayasu s disease has been extensively investigated[1-13] and all hypotheses including the autoimmune theory have been based on non hereditary factors In 1962 Judge and colleagues[14] from the clinical studies on his four cases of Takayasu s disease suggested for the first time the involvement of an autoimmunopathy Itoh[1] in 1966 and Ueda and associates[5] in 1968 postulated the

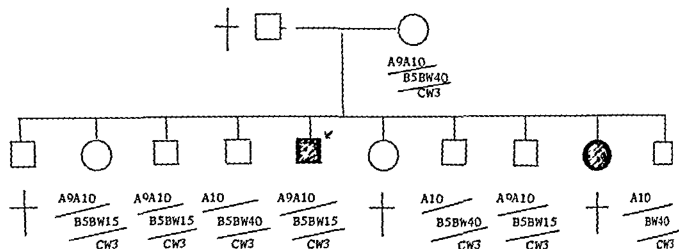


Fig 5 HL A phenotypes of family members in Case VIII

Table IV HL A phenotypes in Takayasu s disease

A locus		A 2	A 9	A 10	A 11	AW33
Takayasu s disease (65)	No patients	23	46	23	8	6
	Frequency (%)	35 4	70 7	35	12.3	9 2
Japanese normals (128)	Frequency (%)	38 3	64 8	11 7	16 4	0 8
	χ	0 2	0 7	15 3	0 6	8 8
p value				10		10 < p < 10

B locus		B-5	B 7	B 12	B 13	BW 15	BW 16	BW 17	BW 22	BW 35	BW-40
Takayasu s disease (65)	No patients	41	2	11	1	10	7	1	8	1	26
	Frequency (%)	6? 1	3 1	16 9	1 5	15 4	10 7	1 5	12 3	1 5	40 0
Japanese normals (128)	Frequency (%)	32.0	16 4	12 5	2 3	11 7	6 3	0 8	14 0	18.8	35 9
	χ	17 0	7 3	0 7	0 1	0 5	1 2	0 2	0 1	11.3	0 3
p value		< 10	10 < p < 10							10	

autoimmune process as determined by clinical symptoms and high titers for antibody against the aortic wall Autoimmunopathy is postulated as being the leading mechanism involved in this morbid condition as clinical characteristics and experimental data satisfy the standard criteria of an autoimmune disease [9] However there are many factors which do not qualify this disease as belonging to an autoimmune classification The lesions are limited and sometimes skipped, and in some patients even in the advanced stage there are no signs of an inflammation Our studies (in preparation) on immune complexes revealed that more than half the number of patients had a negative reaction Thus the immune reactive factor is probably not a primary one in the etiology of Takayasu s disease though this factor may accelerate or modify the condition Judge and associates[18] mentioned femalism and hemodynamic stress ' as factors which accelerate an autoimmunomechanism At the same time they ruled out genetic factors as there was a lack of family incidence in the occurrence of this disease In fact up to that time such occurrences had never been documented However in 1970 Fukaya and co workers[9] reported for the first time a family incidence of Takayasu s disease in which a mother and daughter were both afflicted and since this report, 10 family cases including our own case of twin sisters have been reported in Japan [4] Moreover to our knowledge only two cases of sisters have been documented in Germany and the U S A [2,21] All these cases were reported to be rare and studies from the genetic

Table V Association between HL A–A10 B5 and Takayasu s disease

	HL A–A10		
	Present	*Absent*	*Total*
Patients	24 (36 9%)	41	65
Controls	15 (11 7%)	113	128
Total	39	154	193
Relative risk	= 4 41		
χ^2	= 15.30		
P < 10			

	HL-A–B5		
	Present	*Absent*	*Total*
Patients	41 (63%)	24	65
Controls	41 (32%)	87	128
Total	82	111	193
Relative risk	= 3 63		
χ	= 17 00		
P < 10			

points of view were not done Our examinations of these families revealed that in three the parents were first cousins and HL A typing analyses on the six family members suggested the possible participation of a genetic factor in Takayasu s disease

Population studies also revealed a high frequency of HL A A9 A10 B5 and BW40 in patients with Takayasu s disease A statistical analysis shows the differences between the patient group and the control group with a level of less than 10 (p value) in HL-A A10 B5 As a result these statistically high frequencies of HL A A10 and B5 in patients with Takayasu s disease compared with those in normal Japanese encouraged us to continue this study further to confirm the relationship of HL-A antigens and Takayasu s disease Furthermore it is generally accepted that Japanese American Indians and South Americans have the same frequency of HL A antigens in A and B locus The frequency of B5 antigen is high among Japanese as compared with that in Westerners[23] and both American Indians and South Americans show a high frequency of B5 antigen From this point of view it is very interesting that a haplotype of A9 B5 was frequently encountered in patients with Takayasu s disease At the same time a statistical analysis revealed a low frequency of BW35 in patients with this disease with a level of less than 10 Whether or not such a low frequency of association with a genetic factor is meaningful has to be determined

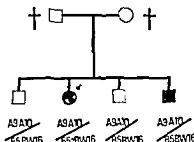


Fig 6 HL-A phenotypes of family members in Case IX

Recent advances in HL A typing analysis make it possible to analyze subgroups of B5 and D locus antigens which are assumed to be situated closer to the disease sensitive gene than B locus antigen[24] We now have direct evidence for the high frequency of an antigen in D locus in Takayasu s disease and such data will be reported in the near future In a previous paper we reported that hyperestrogenism in Takayasu s disease was characterized by high blood levels of estrogens during the follicular period and by low levels of these progesterones in the luteal period and our discussion tended to show that these may be important relative factors in this condition [5, 26] Studies on experimental hyperestrogenism showed that suppression in the metabolism of the arterial smooth muscle induces atrophy necrosis or calcification in the arterial wall Attempts to correct this hormonal imbalance drew attention to the improvement of the clinical symptoms in this disease [8, 29]

Furthermore we confirmed experimentally that estrogen suppresses the level of cAMP content and the high activity of its degradative enzyme cAMP phosphodiesterase in the smooth muscle of the arterial wall[30] Studies on cyclic nucleotides in the serum of Takayasu s disease revealed the high activity of cAMP phosphodiesterase[31]

Recently Meruelo and Edidin observed[1, 33] that the level of cAMP in liver cells of H 2^k mice is higher than that of H 2 and H 2^b mice and suggested that these levels may be regulated by genetic factors In our own studies we observed that the cAMP phosphodiesterase in healthy females who have family members with Takayasu s disease revealed a statistically significant high activity as compared to females from a

family in which the incidence of Takayasu s disease is nil

In a study of systemic lupus erythematosus which is often compared with Takayasu s disease since both have a predilection for women some data suggest the possible association of HL A B8 or B5 with this disease[34 3] and Talal and colleagues[36 37] recently reported the accelerative effect of estrogen and the suppressive effect of testosterone on autoimmune reaction in experimentally induced lupus erythematosus

These data suggest that these endocrinologic disturbances may influence cell function and/or metabolism in such a way as to induce this morbid condition and that genetic factors may regulate all these processes Biochemical, endocrinological, and HL A typing studies are being concomitantly carried out in our laboratory

Summary

Takayasu s disease is characterized by a pulseless condition which most often occurs in young females from Asian or South American areas The cause of this disease remains obscure Recently, we encountered monozygotic Japanese identical twin sisters both of whom were diagnosed as having Takayasu s disease The parents two sisters and one brother are healthy HL A typing analyses revealed that one haplotype found in the father had passed only to these twins Such observations led us to search HL A typing in Takayasu s disease to determine the possible participation of genetic factors in the pathogenesis of this morbid condition

Ten families including that of our own patient have been reported in the literature in Japan as family cases of Takayasu s disease HL A typings in A and B locus analyzed in all family members of six families in attempts to find a common haplotype composed of A9 A10 B5 or BW40 in patients with Takayasu s disease were confirmed statistically ($\chi = 7\ 8$ $0\ 01 < p < 0\ 05$) In a population study HL A typing analyses of 65 patients with Takayasu s disease also revealed a high frequency of HL A A10 and HL A B5 with the level of 15 3 and 17 0 in the χ test ($p < 10$) as compared with the frequency in 128 healthy Japanese These data strongly suggest that a genetic related factor has to be given serious consideration

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The significance of carotid bruits in children: Transmitted murmur or vascular origin, studied by pulsed Doppler ultrasound

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The importance of the auscultatory findings over the neck as well as the precordium was appreciated by an earlier generation of physicians.[1, 2] It is well accepted currently that murmurs characteristic of aortic stenosis are heard at the base of the heart, especially along the upper right sternal border, and that they radiate into the neck.[3, 5] Because of the concerns regarding infective endocarditis[?] and the development of calcific aortic stenosis, the differentiation of the murmur of aortic stenosis from an innocent precordial murmur has important consequences, and prognostic implications.

A cardiac murmur can be heard at one time or another in at least one half of normal children.[6, 8] Similarly, a cervical bruit has a prevalence estimated at 9 per cent to as high as 61 per cent in children.[?] Thus the combination of a precordial murmur and a cervical bruit can be noted very commonly on physical examination in normal children.

The problem is therefore one of accurately differentiating various possibilities inherent with the discovery of a basal ejection murmur which appears to radiate to the neck. Pulsed Doppler echocardiography (PDE) can identify cardiac origins of murmurs.[12, 17] A Duplex Scanner combining a sector scanner and a Doppler flow probe has been used extensively to evaluate peripheral arterial disease.[18, 19] This instrument can be used to identify turbulent flow in the major branches of the aorta. We have employed the two ultrasonic techniques to identify the presence and significance of the combination of a precordial murmur and a carotid bruit.

Subjects and methods

Forty-four patients ages three to 17 years were referred for consultation on the basis of having a precordial murmur and a carotid bruit. In a few patients the diagnosis was known from cardiac catheterization (3) or surgery (3); in the other patients the diagnosis was clinical, reflecting the mildness of their disorder. The patients were examined by two cardiologists with physical examination, chest x-rays, and electrocardiogram. Without knowledge of these results, the patients were evaluated for intracardiac abnormalities using pulsed Doppler echocardiography, which combines M-mode echocardiography with a simultaneous measurement of Doppler shift of reflected ultrasound at a controllable depth within the cardiac structures. Of particular interest was the structure of the aortic valve and turbulence at, below, or above the aortic valve. The same attention was applied to the pulmonic valve (see Fig. 1). The carotid arteries in the same subjects were studied utilizing a peripheral vascular duplex scanner which combines a rotating

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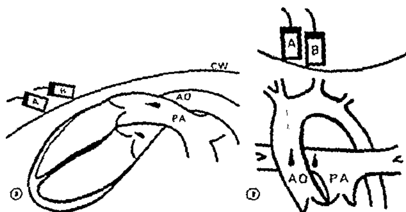


Fig 1A and B A The schematic diagram shows the precordial approach to the flow evaluation of the great vessels Transducer position A shows the sample volume just above the aortic valve and position B shows the volume above the pulmonic valve The M mode images are obtained from this approach in the standard manner CW = chest wall AO = aorta PA = pulmonary artery B This diagram shows the approach to the great vessels from the suprasternal approach for blood flow evaluation Transducer position A shows the sample volume in the ascending aorta and position B shows the volume in the right pulmonary artery The M mode tracings of the great vessels are obtained simultaneously

sector scanner with a simultaneous pulsed Doppler capability The approach to the carotid vessels is shown schematically in Fig 1

The Doppler sampling site (labeled the sample volume) is denoted by a straight line superimposed on the M mode echocardiogram of the PDE as shown in Fig 2 By moving the sample volume (a 1 5 mm × 3 mm teardrop shaped volume) throughout the heart and proximal great vessels blood flow characteristics may be sampled at known sites The audio output from the PDE unit produces a smooth or tonal sound when the flow is smooth or non turbulent and a rough audio signal is produced in the presence of turbulent flow The output also can be recorded as a time interval histogram which indicates turbulent flow by increased bandwidth a wide scattering of dots forming the envelope which outlines the magnitude and direction of blood flow (Fig 2)

The peripheral vascular duplex scanner uses real time B mode imaging (sector scanning) with a 5 mHz pulsed Doppler capability to evaluate flow within the visualized vessels The sampling site for the Doppler measurement is denoted by a bright dot along the line defining the spatial location of the sample volume which is the source of the reflected change in frequency due to flow (Fig 3 A) A light compact ultrasound duplex scanner head permits the operator to rapidly survey vessels of interest and to position the sample volume as desired to assess the character of blood flow within these vessels As with the PDE unit there are two types of output for the Doppler signal including an audio method that is identical to the PDE unit The second output provides a gray scale plot of the frequency content of the Doppler signal versus time Fig 3 B illustrates spectral outputs from flow that is normal and non turbulent The frequency spectrum is relatively narrow with little low frequency content during systole Fig 3C illustrates

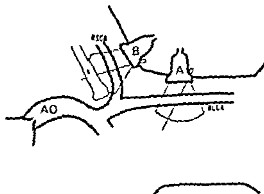


Fig 1C This schematic diagram shows the approach with the peripheral vascular duplex scanner to the right common carotid artery (RCCA) Also shown is the approach to the right subclavian artery (SCA) from the supraclavicular fossa The B mode images (sector scan) and pulsed Doppler ultrasound are obtained simultaneously The sector scan image is denoted by the truncated pie shaped area outlined, and the location of the flow being sampled is denoted by the dot on the straight line transecting the sector scan image

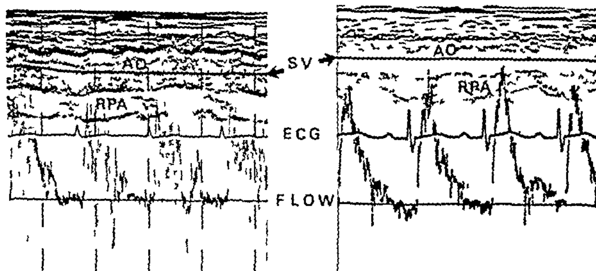


Fig 2 These tracings illustrate the difference between turbulent blood flow *(left panel)* and smooth blood flow *(right panel)* in the ascending aorta as evaluated from the suprasternal notch with pulsed Doppler echocardiography The dots comprising the flow records are closely grouped in the presence of smooth flow *(right panel)* and very scattered in the presence of turbulent flow *(left panel)* This printout is a time interval histogram M mode presentation of the cardiac structures is at the top of the panels showing the aorta *(AO)* right pulmonary artery *(RPA)* and the line indicating where the sample volume *(SV)* for the Doppler evaluation was positioned

turbulent flow characterized by a higher peak frequency coupled with a broad frequency content throughout the cardiac cycle especially during systole

The differentiation between normal and turbulent audio signals is subjective although more sensitive than the time interval histograms and spectral plots While differences between normal and very disturbed flow may be appreciated easily with either audio or visual presentations the differentiation of normal flow from mild degrees of turbulence requires experience and is largely based on the audio signal

Results

On the basis of clinical examination including electrocardiogram and chest x ray 30 patients were thought to have aortic stenosis and/or insufficiency two were thought to have pulmonic stenosis two were thought to have both aortic and pulmonic stenosis and one was diagnosed as having a ventricular septal defect Nine patients were thought to have no heart disease—i e they were judged to have only an innocent murmur coincident with a carotid bruit On the basis of the intracardiac pulsed Doppler examination 28 patients were diagnosed as having aortic stenosis and/or insufficiency three were diagnosed as having pulmonic stenosis and three were concluded to have heart disease other than th above Seven subjects had no intracardiac turbu lence and were concluded to have no heai disease

Table I compares the diagnoses based on clini cal grounds versus the diagnoses based on pulse Doppler echocardiography and the periphera vascular duplex scanner In 30 patients the diag noses were in agreement In 14 there was disagree ment between the diagnoses based on clinica versus ultrasonic methods In those 14 the dis agreement was actually somewhat worse than th table suggests Six patients were diagnosed a having innocent precordial murmurs coinciden with cervical bruits, and four of those were foun to have aortic stenosis by pulsed Doppler echo cardiography all four had abnormal turbulenc at or above the aortic valves two had increase aortic root dimensions, and one was found to hav an eccentric aortic valve orifice One of these fou patients had a murmur which was loudest in th aortic area two had murmurs loudest in th pulmonic area and one had a murmur which wa loudest at the apex The carotid bruit in thes four patients was perceived clinically as loude than the precordial murmur, and the conclusio was drawn that the carotid bruits were no

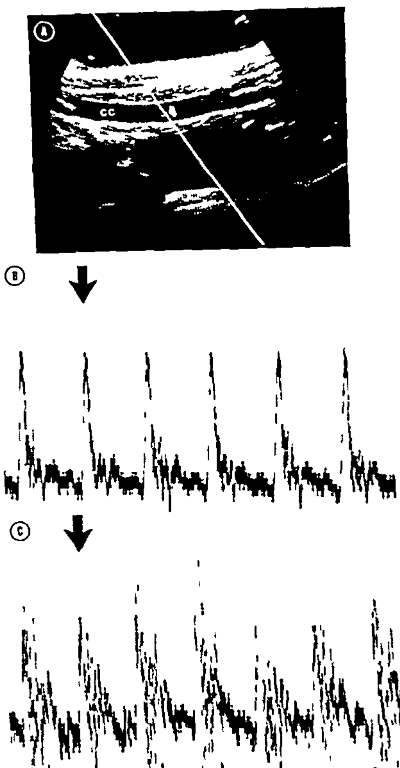


Fig 3 A through C *A* This panel shows a typical image of the common carotid artery with the location of the sample volume denoted by the dot in the straight line transecting the vessel image The common carotid artery *(CC)* is well demonstrated, and the arrow points to the dot showing the location of the sample volume *B* This tracing shows a normal or smooth flow record in the carotid vessel with closely grouped dots in systole The arrow indicates peak systolic flow C This tracing shows an example of a turbulent flow record from the carotid vessel with widely scattered dots in systole

Table I Correlation of the clinical diagnoses and pulsed Doppler echocardiography and duplex ultrasonic scanner evaluation

Diagnosis	*Clinical diagnosis*	*PDE/Scanner diagnosis*
Patients in whom the diagnoses were in agreement N = 30		
AS and/or AI	24	24
PS	1	1
AS and PS	2	2
Innocent murmur & bruit	3	3
Other	0	0
Total	30	30
Patients in whom the diagnoses were not in agreement N = 14		
AS and/or AI	6	4
PS	1	2
AS and PS	0	1
Innocent murmur and bruit	6	4
Other	1	3
Total	14	14
Combined totals	44	44

transmitted from the aortic valve area but were bruits independent of the cardiac murmur From this data two conclusions can be drawn a soft precordial murmur does not rule out aortic stenosis and a murmur that is louder in the neck does not rule out intracardiac disease

Looking at the inverse of this problem we diagnosed six patients as having mild aortic stenosis on the basis of our clinical findings but the pulsed Doppler echocardiogram did not confirm an aortic valvular abnormality Four of these patients had no intracardiac turbulence and two patients had turbulence at the pulmonic valve These six patients had precordial murmurs that were grade II to III/VI in intensity, and murmurs in the suprasternal notch or over the carotids that were of the same intensity We therefore had assumed that the carotid bruits were transmitted from the aortic valve but four of these were only innocent murmurs that were coincident with carotid bruit It is not clear in the patients with pulmonic stenosis whether the intracardiac murmur was transmitted to the cervical region or whether there was a coincidence of the pulmonic murmur and an unrelated carotid bruit

Since much of the interest in carotid bruits stems from the emphasis in the literature on aortic stenosis we examined the relationship of the intensity and precordial location of the cardiac murmur in patients with aortic stenosis confirmed by pulsed Doppler echocardiography and the intensity and location of bruits in the neck by auscultation (Table II) The site of greatest intensity for the ejection murmur was most often the aortic area (11 patients) there were five patients who had a murmur that was equally loud at the pulmonic and aortic areas, and in six cases the murmur was louder at the pulmonic area than at the aortic area In the neck the site of maximal intensity of the bruit was usually at the suprasternal notch or suprasternal notch and right common carotid artery The left common carotid artery was the site of maximum intensity in only one case and in an additional two patients both carotid arteries had equally intense bruits louder than at the suprasternal notch Although there was an over all correlation between the intensity of the precordial murmur and the carotid bruit, there were many individual exceptions including instances in which the bruit in the neck was substantially louder than the precordial murmur and vice versa Obviously it is impossible in these patients with aortic stenosis to prove that the cervical murmurs heard were transmitted from the aortic valve considering the frequent occurrence of relatively loud carotid bruits in the absence of heart disease

The vascular duplex scanner showed turbulence in 42 of the 44 subjects This is not surprising in view of the requirement for inclusion into the study of a carotid bruit by auscultation

Table II Maximal intensity by auscultation of precordial murmurs and neck bruits in 24 patients diagnosed as having aortic valve abnormality confirmed by pulsed Doppler echocardiography

Greatest intensity	Precordial location: Aortic area	Aortic & pulmonic areas	Pulmonic area	LLSB and Apex	Apex	Neck: Supra sternal notch	Supra sternal notch & RCCA	RCCA and LCCA	LCCA
II	3	1	2			2	4†	2	1
II III		1	1		1				
III	2	1	2	1		3	3‡		
III IV	3		1			2			
IV	2	1				2	4†		
IV V	1	1							
V						1			
Totals	11	5	6	1	1	10	11	2	1

* = heard equally well at the apex
† = one heard equally well over the LCCA.
‡ = one heard equally well in all neck areas.

Table III presents the relationship between the cardiac diagnosis and the location of the turbulent flow found by the Doppler examination It is apparent that most subjects who had any cervical bruit were apt to have turbulence in both the right and left common carotid Five of the 40 subjects with vascular turbulence had turbulence found only in the right common carotid artery and only one subject had turbulence found in the left common carotid The findings in patients with aortic stenosis confirm the clinical impression that patients with aortic stenosis usually have carotid bruits Twenty seven out of 28 patients with aortic stenosis had turbulence found by Doppler examination in either the right or left common carotid The one exception was found to have turbulent flow in the right subclavian artery However the Doppler findings confirmed the auscultatory findings that carotid bruits were also compatible with the diagnosis of pulmonic stenosis In fact all three patients with pulmonic stenosis had a carotid bruit and turbulent carotid artery blood flow The findings of turbulence in five of seven normal subjects in the carotid arteries establishes that carotid turbulence is not necessarily transmitted from the heart nor does it mean vascular disease since these are all young healthy subjects who have no atherosclerosis

Discussion

The peripheral vascular duplex scanner and PDE have established that carotid bruits are a genuine phenomenon in children without vascular disease or heart disease and that the bruits are not necessarily transmitted from the heart The scanner also provides anatomic information in addition to the Doppler flow data of primary interest in this study which confirms visually that the vessels are without obstruction

Pulsed Doppler echocardiography is an ideal technique to study patients with minimal disease in whom the risk of invasive studies cannot be easily justified In addition to the anatomic information of conventional echocardiography the PDE unit functions as an intracardiac or intravascular phonocardiogram Although it can establish directionality of flow in addition to

Table III Distribution of vascular turbulence in relation to final cardiac diagnosis

Diagnosis (final)	N	RCCA only	LCCA only	RCCA & LCCA	None
Aortic stenosis (AS)	28	3	1	23	1
Pulmonic stenosis (PS)	3	1	0	2	0
AS + PS	3	0	0	3	0
Normal	7	1	0	4	2
Other ht disease	3	0	0	2	1
Totals	44	5	1	34	4

RCCA = Right common carotid artery LCCA = Left common carotid artery
One each of small ventricular septal defect, mild mitral regurgitation and minimal pulmonic insufficiency

turbulence and velocity of flow there is no way to positively prove transmission of a murmur or bruit although it is possible to show that a bruit is *not* transmitted by showing that there is no turbulence at the cardiac level

The results of our study confirm the conventional wisdom that murmurs of aortic stenosis are usually louder at the second right interspace and that they are almost always associated with a carotid bruit Unfortunately specificity is lacking since pulmonic stenosis also can be associated with carotid bruits and even worse normal subjects with innocent murmurs may appear to have a transmitted murmur when in fact they have only an independent innocent carotid bruit The differentiation is most difficult in the mild cases such as made up the bulk of our subjects The differentiation is much simpler in the more severely involved subjects since the patient with significant pulmonic stenosis will usually have right ventricular hypertrophy on electrocardiogram and post stenotic dilatation of the main pulmonary artery Similarly the aortic patient may show left ventricular hypertrophy and post stenotic dilatation of the aorta and eccentricity of the valve orifice on the conventional echocardiogram

There remains the question as to the importance of differentiating mild aortic stenosis from pulmonic stenosis or an innocent murmur A false positive diagnosis of aortic stenosis can subject the patient to difficulties in obtaining life and health insurance and may prevent him from full participation in athletics and could conceivably result in a cardiac neurosis On the other hand a false negative diagnosis would deprive the individual of protection against infective endocarditis In the past ten years the only two fatal cases of infective endocarditis that have occurred in our patient population happened in patients with minimal aortic stenosis due to a bicuspid aortic valve Both of these patients succumbed in spite of appropriate antibiotic therapy and their example is a compelling argument for accurate diagnosis and appropriate preventive measures Numerically the problem is also substantial Nearly 1 per cent of the normal population have a bicuspid aortic valve which means that approximately two million people in the United States have this disorder On the other side of the coin at least one half of normal children have precordial murmurs and a similar number would appear to have carotid bruits Thus, the population that is at question is a very large one and probably constitutes the most common differential cardiac problem faced by physicians in family practice or pediatrics

The basic question in a childhood population is one of the presence of heart disease particularly mild aortic stenosis A vascular duplex scanner is not necessary for that differentiation, but pulsed Doppler echocardiography is almost essential in our opinion, to distinguish with confidence between a mild degree of aortic stenosis and mild pulmonic stenosis or a normal child with a precordial murmur coincidental with a carotid bruit In the absence of this instrument it would seem provident to continue follow up on the youngsters with precordial murmurs that appear to transmit well to the neck and to minimize problems of infective endocarditis by recommending exceptionally good dental and oral hygiene and appropriate antibiotic coverage at times of potential bacteremia[21]

Summary

Forty four youngsters with precordial murmurs and carotid bruits were evaluated clinically and independently using pulsed Doppler ultrasound The precordial murmur was evaluated with M mode echocardiography combined with Doppler flow evaluation and the carotid bruit was evaluated with peripheral vascular sector scan with Doppler flow evaluation These ultrasonic techniques can identify abnormal blood flow at anatomic sites such as the aortic valve and in the carotid arteries The patients had no symptoms and their condition except for six was mild enough that catheterization was not indicated The clinical diagnosis of aortic stenosis was made in 30 children and nine were thought to have no heart disease On the basis of the ultrasonic examinations 28 patients were diagnosed as having aortic stenosis and seven subjects had no intracardiac turbulence However there was disagreement in 14 instances four of the six clinical normals were found to have aortic stenosis by pulsed Doppler echocardiography six patients diagnosed as having mild aortic stenosis on a clinical basis were found to have no aortic abnormality The results confirm that aortic stenosis usually presents as a murmur maximal in the aortic area which is associated with a carotid bruit Unfortunately in at least one fourth of the

cases the murmur was not maximal at the aortic area and a carotid bruit was found in several normal subjects Since the consequences of over or under diagnosis of aortic stenosis are substantial careful thought should be given to the differential diagnosis and if possible pulsed Doppler echocardiography should be utilized for a definitive statement of aortic valve induced turbulence

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Acute central chest pain in the elderly A review of 296 consecutive hospital admissions during 1976 with particular reference to the possible role of beta-adrenergic blocking agents in inducing substernal pain

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The precise interpretation of acute central chest pain may be straightforward or a formidable diagnostic exercise During the year 1976 296 patients aged 64 to 92 were admitted to acute geriatric medical beds in South Glamorgan via the Emergency Bed Bureau Service due to central chest pain as presumptive cases of myocardial infarction

Patients and methods

All patients had routine 12 lead electrocardiography and blood sampled for creatine kinase (normal range 100 to 200 I U /L) and aspartate transaminase (normal range 5 to 35 I U /L) on reception

The E C G criteria were essentially those of Schamroth and serial changes were considered to be of major importance where the duration of survival was at least seven days Only a peak enzyme level of twice the upper limit of normal or over was accepted as being of relevance in the diagnosis of myocardial infarction for the purposes of this review Further investigations other than a routine biochemical and hematological profile and a chest radiograph were determined by relevant clinical findings

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Results

The final diagnosis is given in Table I

The largest single group of patients with acu chest pain comprised those with confirmato evidence of an acute myocardial infarction Of th 186 patients 70 (37 1 per cent) died confirmi the high mortality rate of acute myocardi infarction in the elderly

Nineteen subjects had had angina varying fro several months to 8 years but admission wa precipitated by an unusually severe attack o pain The maximum duration of pain was 4 minutes but the historical assessment of th duration of pain by elderly patients is often ver approximate All survived No tachyarrhythmi was present during hospitalization but regula ambulant tape monitoring was not available i this department until early 1977 and our mor recent experience indicates that some more sever episodes of angina are associated with transient tachyarrhythmias Only one of these 19 subjects was on a beta adrenergic blocking agent—oxpren olol Transient minor S T depression was record ed by serial electrocardiography in five patients but in none of the 19 subjects were the cardiac enzymes elevated

Ten patients with chest pain had a persistent tachyarrhythmia of 140 minutes or greater requiring specific therapy to control the heart rate Three of these had a previous history of angina

Of the 21 patients diagnosed as having a hiatus hernia or gastro-esophageal reflux the minutiae in the history and the response of symptoms to an

Table I

Myocardial infarction	*Angina*	*Tachyarrhythmia*	*Beta blocking drugs*	*Hiatus hernia*	*Pulmonary infarction*	*Chest infection*	*Others*
186	19	10	35	24	3	5	14

appropriate regime in the absence of E C G and elevated cardiac enzyme evidence of myocardial infarction were considered essential for diagnosis All had confirmatory evidence of a hiatus hernia or gastro-esophageal reflux on barium examination but the radiological frequency of these findings in non symptomatic old people must be emphasized Five patients had acute chest infections in whom central chest pain had caused concern to the family doctor The pain was musculo skeletal in origin in four patients and due to pleural involvement in one patient There were no deaths in any of these non myocardial infarction groups Three patients presenting with central chest pain had a pulmonary infarction with one fatality Fourteen patients with acute central chest pain fell into a mixed group Two died within 14 hours and no satisfactory clinical or autopsy explanation was forthcoming to explain the chest pain two patients had severe aortic stenosis one of whom had a marked iron deficiency anemia two patients had referred pain from cervical spondylosis following a bout of unaccustomed physical activity A cough fracture of a rib Tietze s syndrome acute upper dorsal spinal collapse associated with myelomatosis acute cholecystitis a dissecting aneurysm of the aorta rapid gastrointestinal bleeding following indomethacin consumption and cirrhosis of the liver were the respective cause of chest pain in 7 patients No cause could be found to account for an acute and severe episode of prolonged chest pain in one elderly man

Thirty five patients who were on adrenergic beta blocking agents for periods of 3 to 18 months and who developed severe chest pain in the absence of evidence of infarction of the myocardium call for special comment Forty seven per cent of patients were receiving a beta blocking drug for hypertension and 53 per cent were receiving the drug for the management of angina Pain was intense and had characteristics indistinguishable from the pain of an acute myocardial infarction The duration of pain lasted from 2 to 30 hours The drug was continued by the admitting junior medical staff in 25 cases though discontinued by the senior staff in eight patients at a variable interval after admission Thirty two patients were receiving oxprenolol in doses varying from 40 mg three times daily to 80 mg three times daily Three patients were receiving propranolol in total daily doses of 160 to 240 mg No patient had serial electrocardiographic evidence of a myocardial infarction and all had normal daily levels of serum creatine kinase and aspartate transaminase during a minimum period of 6 consecutive days. One patient had a mild bradycardia of 50 beats per minute No patient had hypotension One patient died two weeks after admission due to severe congestive heart failure and bronchopneumonia Thirty four patients made an uneventful recovery The predominance of oxprenolol in this series appears to reflect the practice of general practitioners in this area to selectively use this drug in the elderly

Discussion

Acute chest pain is a relatively common symptom in the elderly and accounted for 13 per cent of all emergency admissions to the beds of this department in 1976 Sixty three per cent were due to confirmed acute myocardial infarction For the most part other conditions which may mimic a myocardial infarction are widely seen and appreciated Three patients receiving the non beta blocking drug nifedipine for angina are reported to have developed severe chest pain simulating a myocardial infarction[2]

A higher incidence of chest pain due to coronary insufficiency has been recorded in patients on beta adrenergic blocking drugs than in a comparable control group not receiving beta blockers though a possible etiological relationship between these drugs and chest pain was not considered[3] Twelve per cent (35) of our patients on beta adrenergic blocking drugs who presented with substernal pain clinically indistinguishable from myocardial infarction are a group who require urgent recognition Where these drugs were discontinued on admission the maximum

estimated duration of pain was 7 hours In those patients in whom the drugs were discontinued at a variable period after admission the maximum duration of pain was 30 hours Inadequate data were available to establish any relationship between duration of symptoms and duration of post admission administration of beta blockers Serious bradycardia or hypotension was not present

The cause of chest pain in patients receiving beta adrenergic blocking drugs is open to speculation It might be argued that some of these patients were suffering from angina for which they were receiving beta blockers but the prolonged chest pain would seriously question this proposition A fall in cardiac output with diminished coronary perfusion in subjects whose coronary vasculature is already seriously compromised by atherosclerotic disease or associated left ventricular hypertrophy or diminished myocardial contractility leading to increased ventricular volume and wall distension may be pertinent to the production of chest pain in the elderly patients receiving beta adrenergic blocking drugs Since the description of acute myocardial infarction in two patients following abrupt propranolol withdrawal in 1973 several reports of myocardial infarction or acute exacerbation of angina have been reported [13] However symptoms have mainly occurred about 6 days after discontinuing the drug with a range of from 2 to 12 days The sudden onset of chest pain may be attributed to this factor in our patients but none of them had omitted their beta blocking drug prior to hospital admission and in only 10 was the drug discontinued at the time of admission In 17 subjects beta blocking drugs were continued throughout the period of hospitalization

Summary

Two hundred and ninety six patients were admitted to geriatric medical beds in Cardiff in 1976 with acute central chest pain One hundred and eighty six (63 per cent) had a confirmed acute myocardial infarction Of the 37 per cent without evidence of cardiac infarction 32 per cent were on beta blocking drugs The possible role of adrenergic blocking agents in producing acute central chest pain is discussed

I thank my colleagues Dr F L Willington Dr C A R Pippen and Dr D A O Sutton for kindly allowing me access to the records of those patients who were under their care

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Sensitivity and specificity of echocardiography in the assessment of valve calcification in mitral stenosis

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Heavy calcification and poor leaflet mobility in the mitral valve have been recognized as important factors in determining whether a patient undergoing surgery for mitral stenosis should have mitral valve replacement or mitral commissurotomy[1] Although echocardiography has been reported to accurately identify the presence of valvular calcification[2,3] there has been no definite information about the reliability of this technique in determining the degree of calcification M mode echocardiography which has been useful in evaluating mitral valve function[2,4,5] was assessed in this study for its sensitivity specificity and predictive accuracy in identifying and quantifying valve calcification in mitral stenosis

Materials and methods

Eighty seven patients (64 females and 23 males) with pure or predominant mitral stenosis were used in this study including those with associated valvular or coronary lesions The patients ranged in age between 16 and 72 years with a mean age of 50.3 ± 1.4 years (mean $\pm$ standard error of the mean) The diagnosis was confirmed in all the patients by right and left cardiac catheterization (retrograde and/or trans septal left heart technique) utilizing the percutaneous right femoral approach

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Calcification identified by chest x ray and fluoroscopy was graded as heavy light or none respectively when large slight or no densities were identified in the area of the radiological projection of the mitral valve

All the patients had surgical confirmation of the diagnosis at the time of mitral valve replacement or commissurotomy At operation valves were examined by palpation if a closed commissurotomy was performed or by direct visual inspection during open procedures

Pathologic macroscopic and microscopic examination of the resected valve was obtained in 43 of 64 cases of mitral valve replacement Large isolated or diffuse calcium deposits were classified as heavy and light calcifications were considered as small focal areas or flecks of calcium either localized or scattered through the valve The valve was categorized as having no calcium if surgical and/or pathologic examination failed to demonstrate calcium

M mode echocardiograms were performed before operation with a Smith Kline Ekoline 20A Ultrasonoscope interfaced to a Honeywell 1856 strip chart recorder using a 10 cm focused Aerotech transducer More recently a Smith Kline Ekoline 21A Ultrasonoscope connected to a Smith Kline recorder was used The echocardiograms were recorded continuously on light sensitive paper with the transducer on the anterior third and fourth left intercostal space[4] Mitral valve analysis was performed where anterior and posterior leaflets were identified at the point of their maximal excursion

Calcification was graded by previously described echocardiographic criteria that is heavy

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estimated duration of pain was 7 hours In those patients in whom the drugs were discontinued at a variable period after admission the maximum duration of pain was 30 hours Inadequate data were available to establish any relationship between duration of symptoms and duration of post admission administration of beta blockers Serious bradycardia or hypotension was not present

The cause of chest pain in patients receiving beta adrenergic blocking drugs is open to speculation It might be argued that some of these patients were suffering from angina for which they were receiving beta blockers but the prolonged chest pain would seriously question this proposition A fall in cardiac output with diminished coronary perfusion in subjects whose coronary vasculature is already seriously compromised by atherosclerotic disease or associated left ventricular hypertrophy or diminished myocardial contractility leading to increased ventricular volume and wall distension may be pertinent to the production of chest pain in the elderly patients receiving beta adrenergic blocking drugs Since the description of acute myocardial infarction in two patients following abrupt propranolol withdrawal in 1973 [4] several reports of myocardial infarction or acute exacerbation of angina have been reported [5-11] However symptoms have mainly occurred about 6 days after discontinuing the drug with a range of from 2 to 12 days The sudden onset of chest pain may be attributed to this factor in our patients but none of them had omitted their beta blocking drug prior to hospital admission and in only 10 was the drug discontinued at the time of admission In 17 subjects beta blocking drugs were continued throughout the period of hospitalization

Summary

Two hundred and ninety six patients were admitted to geriatric medical beds in Cardiff in 1976 with acute central chest pain One hundred and eighty six (63 per cent) had a confirmed acute myocardial infarction Of the 37 per cent without evidence of cardiac infarction 32 per cent were on beta blocking drugs The possible role of adrenergic blocking agents in producing acute central chest pain is discussed

I thank my colleagues Dr F L Willington Dr C A R Pippen and Dr D A O Sutton for kindly allowing me access to the records of those patients who were under their care

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$$\text{Sensitivity} = \frac{\text{DVC}}{\text{DVC} + \text{NVC}} \times 100$$

Specificity was defined as the number of patients with noncalcified valves (NC) divided by the same number (NC) plus the number in whom noncalcified valves were shown to be calcified by echocardiography or radiography (AC)

$$\text{Specificity} = \frac{\text{NC}}{\text{NC} + \text{AC}} \times 100$$

Predicitive accuracy was defined as the number of patients with detected valve calcification (DVC) divided by the same number (DVC) plus the *number in whom there was a false positive result* (AC)

$$\text{Predictive accuracy} = \frac{\text{DVC}}{\text{DVC} + \text{AC}} \times 100$$

Results

By operative and pathologic evaluation 30 patients were shown to have severe 24 had light and 33 had no calcification of the mitral valve

Table I shows the correlation of the operative finding of heavy light and no calcification with the radiographic previously accepted echocardiographic and derived echocardiographic criteria for calcification The specificity sensitivity and predictive accuracy of each technique or measurement is noted demonstrating that radiography is *the least* sensitive (53 7 per cent) but the most specific (90 9 per cent) and has the highest predictive accuracy (90 6 per cent)

Previously accepted echocardiographic techniques show the highest sensitivity (92 6 per cent) but the lowest specificity (12 1 per cent) and have the lowest predictive accuracy (63 3 per cent) The MT/ST was both sensitive (75 9 per cent) and specific (81 8 per cent) and also had a predictive accuracy (87 2 per cent) similar to that of the radiographic technique Therefore the MT/ST ratio is the single most useful test for evaluating the presence or absence of valve calcification

Table II shows the correlation of the radiographic previously accepted echocardiographic and derived echocardiographic identification and gradation of mitral valve calcification with operative and pathologic findings This table shows that none of the techniques accurately distinguished between heavy and light calcification In general radiographic techniques underestimate the degree of calcification and all echocardiographic techniques tend to overestimate the amounts Therefore since it is probably not useful to quantitate calcification by any currently available technique calcification should be noted only as present or absent

Table II Correlation between radiographic and echocardiographic identification and gradation of valve calcification and operative findings in 87 patients with mitral stenosis

Parameters		*Operative evaluation of mitral calcification* H (30)	L (24)	N (33)
Radiography	H	21	0	0
	L	2	6	3
	N	7	18	30
Echocardiography	H	27	8	4
	L	3	12	25
	N	0	4	4
MT mm	>5	6	1	0
	3 5	24	13	12
	<3	0	10	21
MT/ST	>1 7	24	7	0
	1 5 1 7	5	5	6
	<1.5	1	12	27
BME mm	>15	12	7	2
	10-15	14	4	11
	<10	4	13	20

Total number of cases are shown between parentheses.
H = heavy calcification L = light calcification N = no calcification MT = anteroposterior maximal thickness of the widest echo from the mitral val e MT/ST = r tio between MT and the maximal thickness of the echo from the left v ntricular margin of the interventricular septum BME = m ximal amplitude of the entire band of multipl echoes from the mitral valve.

Discussion

The presence of calcification in the mitral valve has been shown to be *one of the most important* factors in determining whether a patient undergoing surgery for mitral stenosis should have mitral valve replacement or mitral commissurotomy [1] In the past echocardiography was considered to be the most accurate method for evaluating mitral valve calcification [2,3] In this study we proposed to assess the sensitivity and specificity of M mode echocardiography

We found that the previously accepted echocardiographic criteria for evaluating mitral valve calcification were very sensitive but not very specific and were poor in predictive accuracy Therefore we looked for new echocardiographic

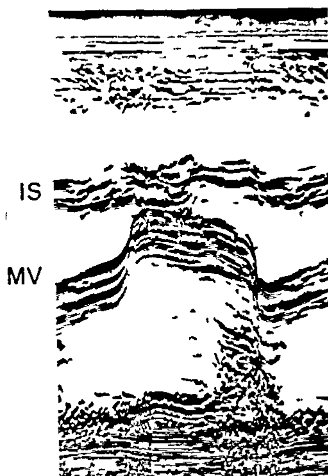


Fig 2 Echocardiogram of a stenotic mitral valve which can be evaluated to be calcific following the usually accepted echocardiographic criteria. The MT/ST ratio is 1 This patient was found to have no calcific mitral valve at operation *IS* = interventricular septum *MV* = mitral valve

criteria and found that of all the echocardio graphic observations measurements and derived indices the MT/ST ratio was the most valuable because it was sensitive (75 9 per cent) specific (81 8 per cent) and had a high predictive accuracy (87.2 per cent) Figs 2 and 3 show two echocardio grams of stenotic mitral valves that meet the usually accepted criteria of light calcification The MT/ST ratio however showed that there was no calcification of the valve and this was later confirmed at operation

Radiography was shown to be the most specific noninvasive technique for determining the pres ence of calcification (90 9 per cent) but it was not very sensitive (53 7 per cent) and had a predictive accuracy of 90 6 per cent Since the presence of any degree of mitral valve calcification predicates the need for mitral valve replacement the ideal test should be very sensitive as well as specific Even though radiography is very specific its lack

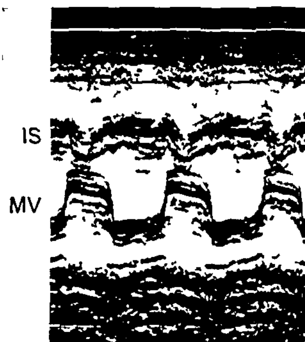


Fig 3 Echocardiogram from a patient with mitral val stenosis The mitral valve can be classified to be calci following the usually accepted echocardiographic criteria Th MT/ST ratio is 1 No calcium was found in the valve operation *IS* = interventricular septum *MV* = mitr valve

of sensitivity indicates the need for another tes The MT/ST ratio comes closest to being the idea test in that it is very sensitive specific and has high predictive accuracy The four echocardio graphic false negative results were found i valves with light and localized calcification Th was probably due to the transducer angulatio which failed to pass the ultrasound beam throug the localized spot of calcium

The 29 false positive results could be explaine by the fact that a fibrotic but noncalcified val can produce many echoes even thick echoes there are surface irregularities and differences i ultrasound impedance between the differer layers of tissue Using the MT measurement an considering positive values equal to or over 3 mm the sensitivity for this echocardiographic param ter in detecting heavy or light calcium was 81 per cent and the specificity was 63 6 per cent I the ratio MT/ST was used the sensitivity (con sidering positive values equal or superior to 1. was 75 9 per cent and the specificity 81 8 per cen If BME parameter was used (considering positi values equal or superior to 10 mm) the sensiti ity was 68 5 per cent and the specificity was 60 per cent (Table I)

Radiography used as a method to further quan

tify mitral calcification was less sensitive (Table II) This was most evident in those with light calcification since there were 18 false negative results (75 0 per cent) in this group confirming the data in a previous report [5]

On the other hand previously accepted echo cardiographic criteria had more false positive results and tended to exaggerate the amounts of light calcification Twenty five of 33 patients (75 7 per cent) with no mitral calcium at surgical and pathologic evaluation showed light calcification and four (12 1 per cent) showed heavy calcification on the echocardiogram (Table II) Eight of 24 patients (33 3 per cent) with light mitral calcification at the anatomical evaluation showed echocardiographic features of heavy calcification

MT values over 5 mm were present only with heavy or light calcification and measurements less than 3 mm were not present in heavy calcification

An MT/ST ratio over 1 7 specifically indicated heavy or light calcification in all the cases and values less than 1 5 were present in only one patient with heavy calcification The BME measurements were less accurate in grading mitral calcium Only measurements over 15 mm were usually present in heavy or light calcification with the exception of two patients who were found to have no mitral calcium on surgical or pathologic examination BME values less than 10 mm were seen in only four of the patients with heavy anatomically document calcification (13 3 per cent) therefore attempts to grade calcification are not warranted by currently available techniques

In our series echocardiographic false negative results were probably due to improper angulation of the ultrasound beam rather than to a deficiency in the technique itself and false positive reports could be accounted for by the severe fibrosis of the valves Although further investigations are needed to improve the accuracy (sensitivity and specificity) of the ultrasound technique the utilization of the indices presented can be helpful in the noninvasive identification and quantification of valve calcification in mitral stenosis and in evaluating its importance in conditioning the surgical decision

Summary

Eighty seven patients (64 females and 23 males) with mitral stenosis were studied by M mode echocardiography to assess the sensitivity and the specificity of the echocardiographic technique in the identification of valve calcification The mitral valves were examined at operation and the amounts of calcium were graded as heavy light or absent We compared this with the amount of calcification assessed by radiographic previously accepted echocardiographic, and newly derived echocardiographic criteria In identifying the presence or absence of valve calcification radiography was the least sensitive (53 7 per cent) but the most specific (90 9 per cent) technique and has the highest predictive accuracy (90 6 per cent) Previously accepted echocardiographic criteria had the highest sensitivity (92 6 per cent) but the lowest specificity (12 1 per cent) and the lowest predictive accuracy (63 3 per cent) The newly derived echocardiographic parameter MT/ST (ratio between the maximal thickness of the left ventricular margin of the interventricular septum) was both sensitive (75 9 per cent) and specific (81 8 per cent) and also had a predictive accuracy (87 2 per cent) similar to that of radiographic techniques The MT/ST ratio is demonstrated to be the most useful non invasive method for assessing valve calcification in mitral stenosis

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Changes in the QRS complex and ST segment in transmural and subendocardial myocardial infarctions A clinicopathologic study

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The electrocardiographic diagnosis of the extent of an acute myocardial infarction (AMI) is often based on the concept that a transmural myocardial infarction (TMI) affects the QRS complex in the electrocardiogram (ECG) while a subendocardial myocardial infarction (SEI) changes the ST T segment [3] Some doubts have however been expressed about the correctness of the differentiation between the TMI and SEI on the basis of the presence or absence of QRS abnormalities [1] Q wave changes have been found in the conventional ECG leads of patients in whom a subendocardial infarction has been found at autopsy [1, 2] Furthermore experimental studies have shown that even slight subendocardial scars can cause QRS changes in the epicardial leads [15] On the other hand autopsy findings have revealed a transmural infarction in subjects whose ECG had shown ST T changes but no QRS signs of an infarction [1, 2] The present study was carried out to compare the ECG findings with respect to QRS and ST T abnormalities in patients who died from an AMI and in whom the extent and location of the ischemic myocardial lesions were verified at autopsy

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Material and methods

The material of this study is part of a greater series of 634 patients admitted to the Kuopio University Central Hospital between March 1975 and May 31 1976 with an acute attack of chest pain An acute MI was diagnosed in 436 of them The WHO criteria for an acute MI were used [2] One hundred fifty six of the patients died during the one year follow up period A postmortem examination which was performed on 106 of them revealed an AMI in 91 patients In the present analysis patients were included on whom an ECG taken at admission as well as within the last 48 hours before death were available Patients with a complete left bundle branch block or with ventricular rhythms were excluded The material was thus composed of 80 patients 56 men and 24 women The age of the men ranged from 36 to 84 years 62 being the mean age and ages of the women ranged from 56 to 85 years with the mean age of 70 years Table I shows the length of the hospitalization period of these patients If an ECG taken during the two week time preceding the admission was available (preinfarction ECG 12 cases) it was compared with the ECG recorded at admission

Electrocardiogram The ECGs were recorded with an ink jet recorder with a frequency response of 0 to 700 Hz (Olli 326 Kone Instruments Helsinki Finland)

The criteria used for QRS abnormalities in

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Table I Length of the hospitalization period preceding the death of the 80 patients who died of an acute myocardial infarction The figures indicate the number of patients

	Less than 24 hours			*1-3 days*			*4 7 days*			*More than 7 days*			*Total number of patients*		
	With scar	*No scar*	*Total*	*With scar*	*No scar*	*Total*	*With scar*	*No scar*	*Total*	*With scar*	*No scar*	*Total*	*With scar*	*No scar*	*Total*
Group I	5	2	7	2	–	2	2	1	3	2	1	3	11	4	15
Group II	3	2	5	7	–	7	1	–	1	2	2	4	13	4	17
Group III	11	7	18	6	6	12	6	1	7	11	–	11	34	14	48
Total	19	11	30	15	6	21	9	2	11	15	3	18	58	22	80

dicative of an acute myocardial infarction were the following

1 a Q wave with a duration of 0 04 sec or more or with a depth of 25 per cent or more of the height of the R wave in the same complex in any of the Leads I II aVF V_1 V_2 V_3 V V V_6

2 a Q wave with the mentioned duration or depth in Lead aVL and the height of the R wave 3 mm or more

3 a Q wave with the mentioned duration or depth in Lead III with a Q wave at least 1 mm deep in lead aVF

4 a QS complex in all the Leads II III and aVF

5 a QS complex in any of the leads V V_3 or V

6 a QS complex in Leads V_2 or V_3 with an R wave of 1 mm or more in the lead to the right from these leads (V_1 or V)

7 a QS complex in all the Leads V V_2 V with the presence of left or right ventricular overloading excluded

8 a Q wave with a duration of 0 04 sec or more in connection with a complete right bundle branch block (CRBBB) in any of the Leads I II aVF V V V_3 V V_5 or V

9 an R wave in Leads V or V_6 lower than 6 mm with a significant pulmonary disease excluded and

10 an R wave higher than the S wave in Lead V with right ventricular hypertrophy excluded

The ECGs were also checked for *other QRS deformities*

1 an r wave lower than 2 mm in leads V or V_7

2 a Q wave of any duration in lead V

3 an R wave in Lead V lower than in V_2

4 the absence of a q wave in all the Leads I V_5 and V_6 septal q wave

5 the presence of a notch during the initial 0 04 sec of the QRS complex in any of the precordial leads or in two of the 12 leads with a duration of 0 02 sec or more in at least one lead and

6 the presence of a notch during the terminal 0 04 sec of the QRS complex in at least two of the 12 leads with the duration of the notch 0 02 sec or more in at least one lead

A definite ST segment depression was considered to be present if the J point was depressed 2 mm or more and was followed by a horizontal or downward sloping ST segment for at least 0 08 sec in one or more of the 12 leads The preceding P Q segment was used as a reference line The depression of the isoelectric line caused by an atrial T wave was noted and its depressing effect on the J point was eliminated[1]

An ST segment elevation was noted in Leads I II III aVL aVF V_5 and V_6 if it was 1 mm or more and in Leads V V_2 V and V_4 if it was 2 mm or more The elevation was compared to the P Q segment

An inverted T wave in Leads I II V_2 V_3 V V_5 and V_6 was noted if it was deeper than 3 mm In Lead aVL an inverted T wave of the same depth was noted if the R wave in the same lead was 5 mm or more and in Lead aVF if the preceding QRS complex pointed predominantly upwards

Autopsy data The macroscopic autopsy study of the myocardiums was performed by a technique modified from one described by Saphir[5] The size and location of an acute and old infarction were estimated In the areas of an acute infarction the myocardium was sectioned perpendicularly to the epicardium in order to determine

Table II Changes in the ECGs taken at admission (see text for definition)

	QRS signs of AMI		*Definite ST segment depression*		*ST segment elevation*		*T wave inversion*	
	Number of cases	*Percentage*	*Number of cases*	*Percentage*	*Number of cases*	*Percentage*	*Number of cases*	*Percentage*
Group I (15 cases)	6	40	8	53	4	27	4	[illegible]
Group II (17 cases)	10	59	9	53	7	41	2	[illegible]
Group III (48 cases)	23	48	23	48	20	42	11	23
Total (80 cases)	39	49	40	50	31	39	17	21

the extent of the lesion An acute lesion limited to the inner two thirds of the thickness of the left ventricular wall was regarded as a subendocardial infarction When the lesion involved also the outermost one third of the left ventricular wall the infarction was transmural The macroscopic myocardial lesions were reconstructed in drawings Conventional histological techniques were used in the microscopic studies of which all were performed by the same pathologist (T R)

On the basis of the autopsy findings the cases were divided into three groups

Group I Fifteen patients with an acute subendocardial infarction in eight cases circumferential in seven cases localized

Group II Seventeen patients with an extensive acute infarction involving four wall segments (anterior lateral and posterior walls of the left ventricle and the interventricular septum) with a transmural penetration in at least one wall

Group III Forty eight patients with an acute localized infarction which was transmural and limited from one to three segments of the left ventricle (anterior lateral or posterior wall or the interventricular septum)

An old myocardial infarction was found in a great majority of the cases in all groups—in 73 per cent of the total series (Table I)

Serum enzyme diagnostics In the serum enzyme diagnoses of an AMI the upper normal limit used for serum aspartate aminotransferase (ASAT or GOT) was 40 U/L +37° C and for serum creatine phosphokinase (CK) 200 U/L +37° C In addition characteristic abnormal serum enzyme curves were needed in order to consider a case indicative of a myocardial infarction Among the patients of whom a serum enzyme curve was available it was abnormal in eight out of the nine cases with an SEI (Group I) and in 45 out of the 48 cases with a TMI (Groups II and III)

Results

QRS complex In the ECGs taken at admission QRS signs of an infarction were found in 40 per cent of the patients with an SEI (Group I Table II) and in 51 per cent of those with a TMI revealed at autopsy (Groups II and III Table II) The ECGs taken during the last two days before death showed QRS changes of an infarction in 53 per cent of the cases with an SEI (Group I Table III) and in 65 per cent of those with a TMI (Groups II and III Table III) The prevalence of the QRS changes in an AMI tended to be higher in patients with an old MI (71 per cent) found at autopsy than in those with no myocardial scars (45 per cent)

The electrocardiographic and autopsy data of the patients with a recent SEI are presented in detail in Table IV QRS signs of an AMI were evident in eight out of the 15 patients in whom a recent SEI was revealed at autopsy An old myocardial scar was found in 11 of them QRS signs of an AMI were found in seven out of the 11 patients with an old myocardial scar and in one out of the four patients with no scar The ECG recorded before admi on QRS abnormalities in four an old MI (cases No 4 7 8 of the four cases w

Table III Changes in the ECGs taken during the last 48 hours before death (See text for definition)

	QRS signs of AMI		*Definite ST segment depression*		*ST segment elevation*		*T wave inversion*	
	Number of cases	*Percent age*	*Number of cases*	*Percent age*	*Number of cases*	*Percent age*	*Number of cases*	*Percent age*
Group I (15 cases)	8	53	10	67	5	33	6	40
Group II (17 cases)	11	65	8	47	8	47	4	24
Group III (48 cases)	31	65	20	42	21	44	8	17
Total (80 cases)	50	63	38	48	34	43	18	23

these cases the QRS changes developed in connection with the recent infarction In addition QRS deformities not fulfilling the infarction criteria developed in five subjects (Cases No 1 4 5 9 and 14 Table IV) and an earlier QRS sign of an infarction disappeared in three patients (Cases No 5 7 and 15 Table IV) Thus there were nine patients with an SEI whose ECG showed depolarization changes which developed together with clinical symptoms and signs of an acute myocardial infarction

ST T segment *A definite ST segment depression* was found in the admission ECGs in 53 per cent of the cases with an SEI (Group I Table II) and in 49 per cent of those with a TMI (Groups II and III Table II) In the ECGs taken during the last two days this pattern was found in 67 per cent of the cases with an SEI and in 43 per cent with a TMI (Table III) The definite ST segment depression in the SEI patients was most common in those with a circumferential subendocardial infarction In these patients this ECG sign was found in seven out of eight cases (87 5 per cent) while in patients with a localized subendocardial infarction it occurred in three out of seven cases (43 per cent) In the latter the sign also appeared in fewer leads than in patients with a circumferential SEI (Table IV)

In cases of an SEI a definite ST segment depression was found in the ECGs taken at admission in seven out of the 10 patients with the pattern also in the last ECG The time interval between the two ECGs varied in different patients from one hour to four days Furthermore in cases with a TMI the pattern was evident in the first ECG in 20 out of the 28 patients with the pattern in the last ECG The time intervals between the two recordings varied from one hour to 19 days

A definite ST segment depression was found in the ECGs of 14 out of the 30 patients who died during the first day In the 50 patients surviving longer than one day this pattern was found in the admission ECG of 24 patients and in the last ECG of 25 patients

A definite ST segment depression with no QRS signs nor an ST segment elevation indicative of a MI was found in five cases with an SEI (33 per cent) (Cases No 1 2 3 5 and 12 Table IV) and in 11 cases with a TMI (17 per cent) Nineteen out of the patients (48 per cent) with a definite ST segment depression had not used digitalis before admission (five patients in Group I three in Group II and 11 in Group III) while 50 per cent of the patients with no ST segment depression had been on digitalis therapy

An ST segment elevation was found in the admission ECGs in 27 per cent of the cases with an SEI and in 42 per cent of the cases with a TMI In the last ECG the ST segment was elevated in 33 per cent of the cases with an SEI and in 45 per cent of those with a TMI (Table III) In the patients with an SEI the ST segment elevation tended to be less frequent than the definite ST segment depression As opposed to the QRS signs of an infarction the ST segment elevation and the definite ST segment depression tended to be less frequent in patients with an old MI than in those with no myocardial scars found at autopsy

Table IV ECG and autopsy findings of the 15 patients with a subendocardial myocardial infarction whose ECG recorded within the last 48 hours was available

		Other QRS deformities			
				Significant QRS notches	
	QRS signs of myocardial infarction	*Minor QRS sign in chest leads*	*Septal Q wave*	*Initial in leads*	*Terminal in leads*
Case 1 55 year-old man	–	Height of *r* wave in lead V 1 mm	absent	V	V V
Case 2 81 year-old woman	–	–	absent	–	–
Case 3 77 year-old woman	–	–	absent	II V	III aVL
Case 4 57 year-old man	Height of R wave in lead V 4 mm	q wave in lead V	absent	V	–
Case 5 72 year-old woman	Disappearance of previous Q wave of infarction in leads II III aVF	R wave in lead V, lower than in lead V	absent	–	–
Case 6 36 year-old man	–	–	present	–	–
Case 7 71 year-old woman	Q wave in lead aVL Disappearance of Q wave in lead V CRBBB present	–	absent	–	–
Case 8 46 year-old man	Q wave in lead V	–	absent	–	–
Case 9 64 year-old man	Q wave in lead V CRBBB present	–	present	–	–
Case 10 70 year-old man	Q wave in lead V and V height of R wave in lead V 2 mm.	–	present	–	–
Case 11 73 year-old man	Q wave in leads II III AVF V V V	–	present	–	–
Case 12 69-year-old woman	–	–	absent	–	–
Case 13 56 year-old woman	Q wave in leads II III aVF QS in V V, V	–	present	–	–
Case 14 47 year-old man	–	–	present	–	III aVF
Case 15 68 year-old man	Disappearance of Q wave in leads II III aVF height of R wave in lead V 3 mm.	–	present	–	V

*The pattern developed with the clinical signs of a myocardial infarction

In 11 patients the ECG showed a definite depression and an elevation of the ST segment (three cases with an SEI and eight with a TMI) In four cases an elevation in the anterior leads was associated with a depression in the inferior or lateral leads In two cases an elevation in the anterolateral leads was combined with a depression in the inferior leads and in five cases an elevation in the inferior leads appeared simultaneously with a depression in the anterior or anterolateral leads

T wave inversions in different groups are shown in Tables II and III In one of the six cases with an SEI the ECG showed a T wave inversion but no QRS sign nor the mentioned ST segment deviations pointing to a myocardial infarction (Table IV) In one additional case of SEI and in five of TMI the ECG showed only slight ST T changes but no definite QRS or ST segment changes of infarction

Discussion

Without doubt the autopsy is the most reliable reference for evaluating the clinical aspects of the

Definite St segment depression in leads	St segment elevation in leads	T wave inversion in leads	Definite abnormal serum enzyme curve	Location of myocardial infarction of the left ventricle	
				Old	Recent
I AVL, V V V	–	I aVL, V V	+	Posterior wall	Septal anterior lateral walls
II III aVF V_n V V	–	–	+	–	Septal anterior lateral posterior walls
I II V V	–	V	+	Posterior wall	Septal anterior lateral walls
I II V V V	–	–	+	Septal anterior walls	Septal anterior lateral, posterior walls
I II aVL, V V V	–	–	not available	Septal, anterior walls	Septal, anterior lateral posterior walls
–	–	V	+	–	Septal anterior lateral posterior walls
II III aVF V_n V_n V	–	–	+	Posterior lateral walls	Septal anterior lateral, posterior walls
II III aVF	V V	V V	not available	Posterior wall	Septal, anterior lateral, posterior walls
II III aVF	aVL, V V	V V	not available	–	Septal anterior walls
V	V V	–	not available	Septal, posterior walls	Posterior lateral walls
–	V V V	–	not available	Posterior wall	Septal, anterior lateral walls
I II aVL V V V	–	V V V	–	–	Septal posterior walls
–	V	–	+	Posterior wall	Septal anterior walls
–	–	–	+	Septal anterior walls	Septal anterior walls
–	–	–	not available	Posterior lateral walls	Septal anterior walls

type and extent of myocardial lesions The majority of the fatal cases of MI represent an extreme stage of ischemic heart disease with extensive old and recent myocardial lesions It is obvious that myocardial scars can produce disortion in the electrical field caused by an AMI [14] Best information of the electrocardiographic changes caused by an AMI could therefore be obtained from patients with no old MI Since the prevalence of myocardial scars is very high in the fatal cases of AMI e g 73 per cent in the present series the number of ideal cases with no old myocardial infarcts in most previous studies has been small [16 2] as was also the circumstance in the present study (22 cases)

The depolarization changes, either definite or so called minor QRS deformities, appeared frequently in the ECGs of patients with an acute subendocardial myocardial infarction Although most of the Q wave changes occured in SEI patients with a scarred myocardium they were also found without an old MI According to *traditional* ECG literature Q wave changes in the ECG do not appear in association with an

SEI[5, 9, 10] Hence opposite findings even in such a small series as the present one give reason for reconsideration The occurrence of depolarization changes in the ECG in connection with an SEI has also been reported by other authors[14, 3, 6, 27]

Obviously the QRS changes appeared in fewer leads and were smaller in size in SEI patients than in those with TMI In cases with a circumferential SEI changes in the subendocardial electrical forces can be deformed or cancelled by electrical forces produced by oppositely located lesions The remote position of the electrodes from the subendocardium tends to lead to the diminishing and disappearance of the subendocardial changes In addition a different conductive capacity in the blood cavity and the myocardium modify the electrical forces causing unexpected changes[14]

QRS changes of MI were missing in 35 per cent of the patients in whom the autopsy revealed an acute TMI Since the last ECG was taken within 24 to 48 hours before death in a number of cases it is possible that in some cases the acute myocardial lesion had still progressed after the recording One third of the patients died during the first day in hospital In many of them the lesion had probably not been fully developed at the time of the recording It has been stated that a scar in the opposite wall of the left ventricle can cause cancellation of the QRS forces produced by an MI[1] This explanation however does not seem likely in the present study since the Q waves were missing more often in patients with no old MI than in those with a scarred myocardium

The prevalence of the definite ST segment depression was high in the present series It seems to be a characteristic ECG finding particularly in association with a circumferential SEI but it also occurred in association with a more localized subendocardial lesion and TMI Some of the ST segment depressions are of course reciprocal changes in the ST segment elevation due to injury in the opposite wall However the ST segment depression frequently appeared in leads adjacent to the leads with an ST segment elevation or even without an elevated ST segment The selected nature of the postmortem series with a high prevalence of cases with an extensively damaged myocardium obviously increased the prevalence of this ECG finding The preliminary results from a one year follow up of the original series suggest that the prognosis of patients with definite J point and ST segment depressions found in the acute phase of MI is worse than that of patients with no definite ST segment depression[28] Furthermore the results from an other autopsy series indicate that about 70 per cent of fatal cases of hospital patients with a definite ST segment depression in ECG suffer from an acute phase of MI[4]

It is well known that the ST segment depression in the ECG occurs in the presence of subendocardial injuries[29, 21, 26, 31] Transient myocardial ischemia due to an emotional or a physical stress can also cause an ST segment depression of this kind in patients suffering coronary disease[32, 5] A specific shape of an ST segment depression is indicative of certain conditions for example left ventricular strain digitalis effect or hypokalemia[14, 35, 36] However the J point is only slightly depressed in these cases[35] Since the prevalence of patients using digitalis before hospital admission was in the present series about the same in patients with or without an ST segment depression and since a definition based on the J point depression was used it is improbable that digitalis could have played a significant role in the genesis of the ST segment depression as defined in this study

According to our results we have good reason to conclude that an SEI can not always be distinguished from TMI on the basis of the presence or absence of the QRS changes in ECG QRS abnormalities of MI may be lacking in even one third of transmural lesions and on the other hand they may develop in patients with the infarction limited to the subendocardial layers A definite ST segment depression in several leads in association with an acute chest pain attack suggest the presence of a circumferential subendocardial lesion The pattern is however not an uncommon finding in patients with a more localized SEI or even TMI and apparently is in this connection an indicator of a severe ischemia of the myocardium outside the infarcted area

Summary

The QRS complex and ST segment in the ECGs of 80 patients who died of an acute myocardial infarction (MI) were studied in relation to the extent of the MI (subendocardial vs transmu

ral) Changes in the QRS complex developed in nine out of the 15 cases with an acute subendocardial MI Five of these cases fulfilled the conventional QRS criteria for a myocardial infarction

A definite ST segment depression (a J point depression of 2 mm or more in at least one lead and a horizontal or downward sloping ST segment with a minimum duration of 0 08 sec) occurred most frequently in connection with a circumferential subendocardial MI (88 per cent) but it was also found in a regional subendocardial (43 per cent) and transmural MI (43 per cent) In 17 per cent of the cases with a transmural MI this was the only ECG abnormality It is concluded that cases with a subendocardial MI cannot always be distinguished from transmural MI on the basis of the presence or absence of the QRS changes and that an ST segment depression as defined in this study can give additional information in the evaluation of an acute phase of an MI

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Experimental and laboratory reports

Electrocardiographic and serum enzymic alterations associated with cardiac alterations induced in dogs by single transthoracic damped sinusoidal defibrillator shocks of various strengths

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Ideally an electric shock for cardiac defibrillation stops fibrillation without damaging the heart We now know that the shock strength necessary to defibrillate is a function of body weight[1,2] and that shocks of high current and energy can produce cardiac damage[3-5] However no reported study has quantitated the safety margin between defibrillation threshold and damage threshold Such data are important for more effective use of present defibrillators and for the design of new equipment

This study was designed to quantitate some of the changes produced in non fibrillating hearts of dogs by transchest damped sinusoidal electric shocks of various suprathreshold strengths and to calculate the safety margin by comparing these data with the defibrillation threshold previously published for dogs The diagnostic and prognostic value of ECG s and the serum activity of certain isoenzymes for cases of myocardial infarction is well accepted but the value of these tools in analysis of damage from transchest defibrillation has received limited study[6] Therefore ECG changes and serum concentration of cardiac isoenzymes were analyzed as potentially useful indicators of the occurrence and severity of myocardial morphologic damage from electric shock.

Methods and materials

The 56 male and female mongrel dogs (2 4 to 15 kilograms body weight) were classified into eight groups depending upon the shock strength each received (Table I) In every case one transchest damped sinusoidal shock was administered and the ECG was monitored during the next two hours In 25 dogs serum levels of LDH α HBDH and CPK activity were measured immediately before the shock and every 30 minutes for 2 hours after shock Also in the same animals a qualitative MB CPK analysis was included at these times Some dogs were allowed to survive longer than two hours (1 2 4 14 or 56 days) to study the sequential cardiac morphologic alterations The details of the sequential morphologic changes are reported elsewhere

Preparation for electric shock A five minute preshock ECG was recorded from each dog in the standing position The dog was then weighed anesthetized with pentobarbital sodium (30 mg / Kg body weight intravenously) intubated placed in the supine position on a surgery table and a second five minute preshock ECG was then recorded

Defibrillation electrodes (diameter 10 cm) were applied to areas of the dog s chest that had been shaved The electrodes were coated with low resistivity electrode paste One electrode was

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Table II Effect of shock strength on mortality and incidence and severity of cardiac morphologic damage produced by trans chest application of damped sinusoidal shocks to dogs in the absence of fibrillation *Numbers in parentheses indicate number of subjects exhibiting the phenomenon divided by total number of dogs in the group*

Damped sinusoidal peak current do e in A /Kg (ingl shock)				*Incidence of mortality within two hours*		*Incidence of gross damage in animals surviving two hours or more*			*Incidence of microscopic damage in animals surviving two hours or more*		
Target dose	*Average of delivered dose*	*Range of delivered do es*	*Average delivered energy in joules /Kg*	*%*	*No of dogs that died/ total dogs*	*%*	*No of dogs affected/ total dogs*	*Mean severity index*	*%*	*No of dogs affected/ total dogs*	*Mean severity index*
0	0	0	0	0	(0/4)	0	(0/4)	–	0	(0/4)	–
1	0 9	0 7 1 0	1 0	0	(0/5)	0	(0/5)	–	0	(0/5)	–
3	? 7	2 6 2 9	8 5	0	(0/5)	0	(0/5)	–	20	(1/5)	1 0
6	6 0	͵7 6 2	30 6	0	(0/5)	40	(2/5)	1 0	40	(2/5)	1 0
9	8 ,	8 0-9 0	56 0	0	(0/5)	40	(?/5)	1 5	40	(2/5)	1 0
12	12 1	11 6 12 6	107 0	??	(2/9)	⁻1	(5/7)	2 0	71	(5/⁻)	1 6
15	15 8	14 2 17 9	152 0	22	(4/18)	⁻9	(11/14)	2 5	86	(1?/14)	2 0
20	20 ⁻	19 5 2? 6	200 4	20	(1/5)	100	(4/4)	3 0	100	(4/4)	2 0

Severity u dex the calculated ave age alue from all d gs in a group using the scale of 1 0 = mild damag 2.0 = mod rate damag 3 0 = marked damage (see t xt)

and photographed Tissue samples were taken for light and electron microscopic studies Details of these procedures are reported elsewhere Quantitation of the cardiac damage was based on the findings of gross and histopathologic study Damaged tissue was apparent as pale areas in the ventricular myocardium The severity of gross damage was classified as mild (+) if the ventricular lesion was less than 0 5 cm in diameter and less than 2 mm deep Damage was considered moderate (++) if the lesion was 0 5 to 2 0 cm in diameter and 2 mm to ⅓ of the ventricular wall thickness deep Damage was considered to be marked (+++) if the lesion was greater than 2 cm in diameter and the depth of the lesion was from ⅓ to full wall thickness The microscopic damage was semiquantitated by study of 22 blocks of tissue taken from standard sites in each heart (10 from the left ventricular free wall seven from the right ventricular free wall three from the ventricular septrum and one from each of the atria) The damage was graded as mild if there was necrosis of myocardial fibers or an epicardial reaction in fewer than five blocks moderate if either lesion was present in five to 10 blocks and marked if either lesion was present in more than 10 blocks A severity index for gross and microscopic damage was calculated by assigning a value of 1 for mild injury a value of 2 for moderate injury and a value of 3 for marked injury The average score of all dogs in a group was the mean severity index For example if in a group of five dogs marked gross injury occurred in three subjects each would be assigned a value of 3 and if mild injury occurred in two other subjects each of them would be assigned a value of 1 The mean severity index of these five subjects would be

$$2\ 2 = \frac{(3 \times 3) + (2 \times 1)}{5}$$

Results

Mortality Eight of the 56 dogs died after shocking each of the eight had received a shock of 12 or more A /Kg (Table II) Six of these dogs died within a few minutes of the shock one died 36 minutes after the shock and one was found dead 18 hours after the shock. Of the six dogs that died soon after the shock four died from ventricular fibrillation The post shock ECG of one of these dogs (which received 12 6 A /Kg) displayed only ventricular fibrillation after shock The ECG s of the other three dogs (which received

Table III Effect of shock strength on the incidence of transient (within 2 hours after shock) ECG changes

Damped sinusoidal peak current dose in A/Kg (single shock)	Incidence of premature ventricular contraction and/or ventricular tachycardia %	No	Incidence of ventricular tachycardia %	No	Average duration of ventricular tachycardia	Incidence of atrial fibrillation %	No	Incidence of total A V block %	No	Average duration total A V block	Incidence of S T segment changes %	No	Incidence of T wave changes %	No
0	0	(0/4)	0	(0/4)	0	0	(0/4)	0	(0/4)	0	0	(0/4)	0	(0/4)
1	20	(1/5)	0	(0/5)	0	0	(0/5)	0	(0/5)	0	0	(0/5)	0	(0/5)
3	20	(1/5)	20	(1/5)	25 sec	0	(0/5)	0	(0/5)	0	0	(0/5)	0	(0/5)
6	80	(4/5)	20	(1/5)	75 sec	0	(0/5)	40	(2/5)	7 sec	20	(1/5)	0	(0/5)
9	100	(5/5)	60	(3/5)	9 2 min	0	(0/5)	80	(4/5)	39 sec	80	(4/5)	0	(0/5)
12	100	(7/7)	57	(4/7)	7 1 min	14	(1/7)	100	(7/7)	103 sec	57	(4/7)	0	(0/8)
15	100	(15/15)	100	(14/14)	7 9 min	7	(1/14)	100	(14/14)	118 sec	60	(9/15)	47	([illegible]/15)
20	100	(4/4)	100	(4/4)	10 2 min	75	(3/4)	100	(4/4)	166 sec	100	(4/4)	100	(4/4)

All dogs with T wave changes had morphologic damage

shocks of 15 5 15 5 and 16 1 A/Kg) displayed irregular ventricular tachycardia that lasted 23 55 and 76 seconds respectively before ventricular fibrillation began The other two dogs (which received 17 2 and 19 5 A/Kg) died from total mechanical and/or electrical asystole

The dog which died at 36 minutes after shock exhibited a gradually developing hypotension as determined by the femoral artery pulse becoming so weak it could not be palpated and at 36 minutes after shock the heart rate slowed and progressed to asystole

Necropsy of the dog that had been found dead 18 hours after shock indicated only mild to moderate damage of the heart and no apparent cause of death It was assumed that this dog probably died either from a fatal cardiac arrhythmia or from cardiac failure

Cardiac morphologic damage Grossly observable cardiac damage was seen in some dogs that received shocks of 6 or more A/Kg The damaged tissue appeared as pale areas in the free walls of the ventricles within areas that had been in the transthoracic pathway between the electrodes The incidence and severity of the gross damage increased as the shock strength increased (Table II) until all dogs that received the largest dose (20 A/Kg) and survived at least 2 hours had grossly observable marked damage Microscopic damage was seen in some dogs that received 3 or more A/Kg and this too increased in incidence and severity as the shock strength increased (Table II), until all dogs that received 20 A/Kg and survived at least 2 hours had moderate myocardial damage

Electrocardiographic changes ECG changes were observed after all shocks No changes were seen in the electrocardiograms prior to shock or in the non shocked animals

Five types of changes were seen in records of shocked animals (1) premature ventricular contractions (PVC) or ventricular tachycardia (2) atrial fibrillation (3) A V block (4) S T segment elevation or depression and (5) T wave changes All of these were observed in some animals during the first two hours after shock Only PVCs or ventricular tachycardia S T segment changes and T wave changes were observed during the 1 to 56 day post shock period (Table III)

Transient ECG changes during the two hours post shock In general the incidence and duration of the ECG changes increased as shock strength increased up to the 9 A/Kg dose For example a dog given a 6 A/Kg shock had five PVCs whereas a dog given a 15 A/Kg shock had 50 PVCs The most sensitive ECG alteration in response to electric shock was the occurrence of PVCs or ventricular tachycardia These were observed in at least one dog in every shocked group and in every dog which received a dose of 9 A/Kg or more Total A V block was the next

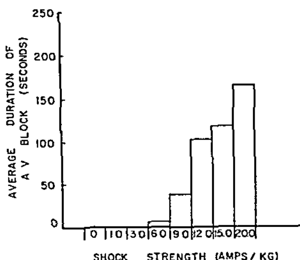


Fig 1 Average duration of total A V block in each group of subjects.

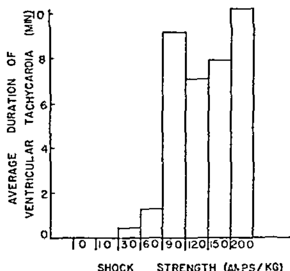


Fig 2 Average duration of ventricular tachycardia in each group of subjects.

Table IV Effect of shock strength on the incidence of persistent (1 56 days) ECG changes

Damped sinusoidal peak current doses in A /Kg (single shock)	*PVCs or V Tach*		*S T segment changes*		*T wave change*	
	%	*No*	*%*	*No*	*%*	*No*
0	0	(0/3)	0	(0/3)	0	(0/3)
1	0	(0/3)	0	(0/3)	0	(0/3)
3	0	(0/4)	0	(0/4)	0	(0/4)
6	0	(0/4)	0	(0/4)	0	(0/4)
9	0	(0/4)	0	(0/4)	0	(0/4)
12	20	(1/5)	0	(0/5)	0	(0/5)
15	82	(9/11)	36	(4/11)	18	(2/11)
20	66	(2/3)	33	(1/3)	0	(0/3)

Table V Incidence of isoenzyme elevation in dog groups given a single shock of 9 to 20 A /Kg

Damped sinusoidal peak current dose in A /Kg (single shock)	*Incidence of MB CPK activity in serum within 2 hours post shock*		*Incidence of twofold rise of serum α 1 LDH activity value greater than 25 μ/L within 2 hours post shock*	
	%	*No*	*%*	*No*
9	0	(0/5)	0	(0/5)
12	25	(2/8)	12	(1/8)
15	33	(3/9)	55	(5/9)
20	100	(4/4)	100	(4/4)

most sensitive indicator of shock strength It was never observed in animals receiving less than 3 A /Kg but was observed in all animals receiving 12 or more A /Kg

A change from control (pre shock) record of the S T segment of at least 0 2 mV in one lead or 0 1 mV in each of the two leads were considered to be significant These were not observed in animals receiving up to 3 A /Kg but changes were observed in a progressively higher percentage of animals as shock strength was increased above that level T wave inversion occurred only in animals that received 15 or 20 A /Kg and occurred in all animals that received the largest dose 20 A /Kg All dogs with T wave changes had morphologic damage Only one atrial arrhythmia (atrial fibrillation) was observed and this occurred only after shocks of 12 or more A /Kg The incidence of early arrhythmias increased with shock strength up to 9 A /Kg at this shock intensity and above this shock intensity all dogs exhibited an abnormal ECG The duration of the ECG changes could be correlated with the shock strength only for A V block (Fig 1) and ventricular tachycardia (Fig 2)

Persistent ECG changes between 1 and 56 days post shock The three ECG abnormalities that persisted for 1 to 56 days after shock were (1) premature ventricular contractions or ventricular tachycardia (2) S T segment changes and (3) T wave changes Some or all of these changes were observed in records from some animals that re

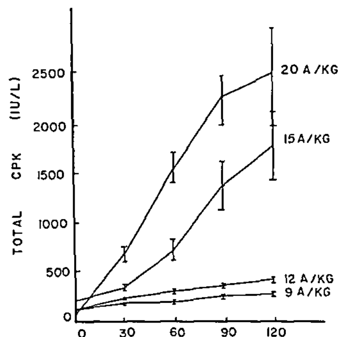


Fig 3 Mean serum concentration of total CPK measured before shock and at 30 60 90 and 120 minutes after shock *Bars* indicate one standard deviation

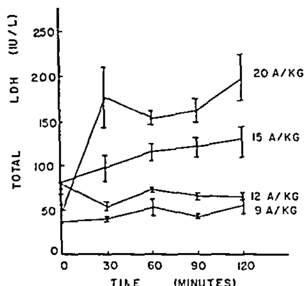


Fig 4 Mean serum concentration of total LDH measured before shock and at 30 60 90 and 120 minutes after shock *Bars* indicate one standard deviation

ceived shocks of 12 or more A /Kg (Table IV)

There was considerable variability in the incidence and duration of ECG changes between 1 and 56 days post shock Only one animal in the 12 A /Kg group showed any ECG change (which was a single premature ventricular contraction) during the 5 minute ECG record taken 24 hours post shock The ECG abnormality of longest duration was T wave inversion in a dog in the 20

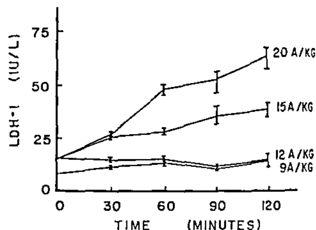


Fig 5 Mean serum concentration of α 1 LDH measured before shock and at 30 60 90 and 120 minutes after shock *Bars* indicate one standard deviation

Table VI Relationship of peak α 1 LDH activity within 2 hours post shock to shock strength and severity of cardiac morphologic damage in individual dogs

Peak cardiac α 1LDH activity (I U /L)	*Shock strength A /Kg*	*Gross damage*	*Microscopic damage*
125	16 1	+ + +	+ + +
125	12 0	+ + +	+ +
110	22 6	+ + +	+ +
100	19 9	+ + +	+ +
6[illegible]	17 6	+ + +	+ +
6[illegible]	14 8	+	+ +
40	14 8	+ + +	+ +
40	21 7	+ + +	+ +
30	15 8	+ + +	+ +

Code + + + = marked damage + + = moderate damage + = mild damage

A /Kg group The T wave inversion appeared 24 hours post shock and persisted until 6 days post shock On day 7 it had returned to control (pre shock) configuration

Maximum duration in any single dog for the other ECG abnormalities were occasional PVCs—3 days ventricular tachycardia—2 days and S T segment changes—2 days All dogs with ECG changes persisting for 24 hours or more after shocking had morphological evidence of damage On the other hand many dogs with morphologic damage had no ECG changes at 24 hours or later after shock

Serum enzyme changes Serum activities of serum CPK total LDH and the α 1 isoenzyme of

LDH and the presence of the MB (cardiac) fraction of CPK were measured only in samples taken from dogs that had received 9 or more A/Kg The mean activities of total CPK total LDH and α 1 LDH at 2 hours after shock were increased and were greatest in groups given largest shocks (Figs 3 4 and 5) The incidence of detection of serum α 1 LDH AND MB isoenzyme of CPK in the serum also increased with shock strength (Table V) However extent of enzyme activity elevation of individual dogs did not correlate well with the severity of morphologic damage (Table VI)

Discussion

The findings of the present study are consistent with clinical reports of complications following electric cardioversion as reviewed by Resnekov[9] (i.e. increased serum enzymes hypotension ECG changes pulmonary and systemic embolism ventricular arrhythmias and increased heart size associated with pulmonary edema) The incidence of all these complications increased when stronger shocks were used for human cardioversion Unfortunately there are no data on man relating the severity of shock induced cardiac morphologic changes to shock strength

In the present study strong damped sinusoidal shocks applied to dogs produced a variety of undesirable effects High electric current strengths were often followed by death cardiac morphologic damage ECG changes and elevated levels of serum cardiac isoenzymic and total serum enzymic activities Incidence of death and the incidence and severity of morphologic damage increased with increasing shock strengths

However a safety margin was demonstrated between the previously reported effective defibrillation dose in dogs (1 A/Kg of body weight) and the dose required to produce significant cardiac morphologic damage cardiac isoenzyme elevation or death

Transchest single damped sine wave shocks did not produce microscopically detectable cardiac damage in dogs until a threefold (over defibrillation threshold) current overdose was applied No gross lesions were observed until a sixfold current overdose and no deaths occurred until a twelvefold current overdose Progressive increases in shock strength above these levels were accompanied by increased incidence and severity of side effects

Many post shock transient ECG changes (A V block atrial fibrillation PVCs ventricular tachycardia S T segment elevation) were observed either with or without demonstrable gross or microscopic morphologic damage The presence of arrhythmias immediately after shock without morphologic damage is not surprising Pansegrau and associates' demonstrated that autonomic nervous system reflex activity after electric shock may result in production of arrhythmias and also may alter peripheral and central hemodynamics These data suggest that transient ECG changes following cardiac shock frequently are not manifestations of cardiac morphologic damage due to the shock T wave changes any time after shock or any ECG change persisting for 24 hours or more in a particular dog was always associated with morphologic damage but the persistent ECG changes were not very sensitive indicators of damage

There was positive correlation observed between shock strength and (1) incidence of post shock mortality (2) incidence and severity of morphologic damage (3) incidence and severity of ECG abnormalities and (4) extent of enzyme elevation Therefore one might expect positive correlation between the four measured dependent variables Such a correlation was not possible for several reasons First a complete set of measurements could not be taken in dogs which died soon after shock and presumably were the most severely damaged Second the early (2 hr) ECG changes were so sensitive to transient autonomic nervous system reflexes that dogs with no damage or mild damage exhibited ECG changes at the safe relatively low (1 to 9 A/Kg) doses Third changes in S T or T wave vector forces of the ECG are better indicators of lesions located in one area of the heart than of symmetrical lesions on opposite sides of the heart Since the damage produced by defibrillation is frequently located almost symmetrically on both sides of the heart there may be little or no net loss of electromotive forces of the ECG

The lack of sensitivity for persisting ECG changes to reflect morphologic damage is also probably due to the location of lesions on both sides of the heart which could result in cancellation of QRS and T wave vector forces and hence no change would be observed

Correlation of morphologic damage with cardiac isoenzyme changes and persistent ECG

changes was possible in that elevated enzyme levels occurred only in dogs with cardiac morphologic damage However correlation was not possible to the extent of measuring positive correlation coefficients probably because of the relatively small mass of cardiac tissue which was destroyed by the shocks Perhaps larger enzyme changes would occur with larger lesions The total LDH and CPK serum elevations reflect damage to non cardiac as well as to cardiac tissue In fact the isoenzyme elevations could have some non cardiac component since the gastrointestinal tract of the dog contains significant quantities of MB CPK[6] Ehsani and colleagues have also reported elevation of the MB fraction of CPK and cardiac necrosis in dogs after multiple high energy shocks but found little elevation of cardiac CPK in humans following atrial cardioversion

Thus when strong shocks were given that resulted in cardiac damage accurate quantitation of the severity of damage was possible only by direct morphologic examination Although T wave inversion or elevated serum α ILDH or MB fraction of CPK always indicated cardiac morphologic damage these changes were not very sensitive to detect mild degrees of cardiac morphologic damage We do not believe that transient changes in the ECG necessarily indicate an undesirable effect of countershock and in fact these changes may be due to an appropriate response of the autonomic nervous system and thus reflect a protective and desirable response to defibrillation On the other hand persistent changes appear to indicate electric shock damage

In summary transient ECG changes occur frequently after defibrillator shocks regardless of the extent of morphologic cardiac damage and they have little value as indicators of damage Persistent ECG changes or elevation of serum cardiac isoenzyme activity are valid indicators of morphologic damage but are not sensitive enough to detect mild damage to the heart

Summary

The safety margin between the strength of shock needed to defibrillate the ventricle and shocks which produce cardiac damage has not previously been reported This study quantitates the shock intensity required to produce ECG alterations serum α ILDH and MB CPK isoenzyme elevation and m[illegible]ardial damage using single transchest damped sinusoidal defibrillator shocks Shocks of 1 to 20 amperes per kg of body weight were applied Fifty six dog weighing 24 to 15 kilograms were shocked with defibrillator pulses via 10 centimeter diameter electrodes applied to the thorax Electrocardiograms were taken to be analyzed for arrhythmias ST segment changes and T wave changes Serum enzyme levels were determined in 25 dogs Macroscopic and histopathologic studies were conducted on the hearts Transchest single damped sine wave shocks did not produce microscopically detectable cardiac damage until at least a threefold current overdose was applied No macroscopic morphologic alterations were observed until at least a sixfold current overdose was applied and no deaths occurred until a twelvefold or greater current overdose was delivered Incidence and severity of ECG changes increase in serum enzyme activity incidence and severity of cardiac damage and incidence of mortality all correlated positively with shock strength However these four adverse effects did not correlate well with each other Transient ECG changes were very frequent following shock application regardless of the morphologic damage produced and hence the transient changes have little value as indicators or predictors of damage Persistent ECG changes were predictive of morphologic changes but were not sensitive enough to detect damage in mildly injured hearts Likewise elevated serum cardiac isoenzyme activity was a reliable but insensitive indicator of damage

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The normal anatomy of the atrial septum in the human heart

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The human atrial septum has assumed an increased clinical importance in recent years because of advances in non invasive diagnosis[1,2] palliative or corrective procedures for congenital and acquired heart disease[3,4] and investigations of conduction tissue pathways and morphology[5-7] In spite of this clinical interest previous anatomical and embryological descriptions have not defined the shape or margins of the mature septum The present study was undertaken to correct these deficiencies

Materials and methods

Ninety human heart specimens were fixed in formalin and transferred to Kaiserling s solution Eight specimens were from infants under 1 year of age 18 were from children between 1 and 10 years of age and 64 were from older children and adults up to 70 years of age

The margins of the atrial septum and fossa ovalis were identified from both right and left atrial aspects by transillumination and by placement of pin markers With the septum under uniform tension in its natural anatomic curvature the margins were marked on the specimens with ink and were transferred successively to transparent and graph paper All linear and area measurements were made from the graph paper

Identification of the anterior margin was facilitated in some specimens by dissection into the fatty tissue between atrial wall and aorta (Fig 1)

Margin identification was most difficult in the superior portion of the septum adjacent to the superior vena cava because the septum was very thick and its transition to free wall was a gradual curvature The most posteroinferior portion of the septum presented similar problems of margin identification because of contributions from the posterior extension of the crista terminalis and the anterior wall of the coronary sinus The margin of the fossa ovalis was easily identified in most hearts because the fossa ovalis was thin and membranous and transilluminated easily In some children s and adults hearts however the margin of the fossa ovalis was harder to identify because its thickness was supplemented by muscle strands from the free wall of the left atrium described previously by Patten[7] which caused it to transilluminate poorly

To determine if any significant changes occurred during the fixation process we studied 12 fresh hearts from one year old pigs whose atrial septa were essentially identical to the human Although the area of the septum was reduced as much as 23 per cent after fixation in 3 per cent formol the shape of the septum and its relation to adjacent structures remained the same In most previous studies[1-4] the term limbus has referred to a significant portion of the margin of the fossa ovalis In this study only the prominent ridge that remains unfused in patent foramen ovale is so designated (approximately one fourth the circumference of the fossa ovalis)

Results

When viewed from the right atrium the atrial septum was a blade shaped structure with three margins (Figs 1 and 2) The tip of the blade was

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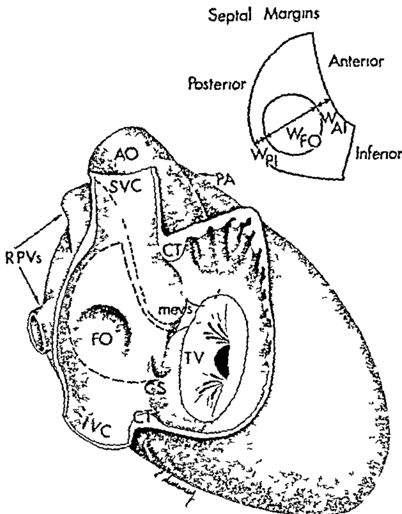


Fig 1 Right atrial view of normal atrial septum *(heavy broken line)* Position of aorta *(Ao)* is indicated by *light broken line* *CS* coronary sinus *CT* crista terminalis *FO* fossa ovalis *IVC SVC* inferior and superior vena cavae *mevs* membraneous ventricular septum *PA* pulmonary artery *RPVs* right pulmonary veins *TV* tricuspid valve W_{AI} W_{PI} W_{FO} width of anterior and posterior isthmi fossa ovalis

directed into the orifice of the superior vena cava The slightly concave anterior margin outlined the curvature of the adjacent ascending aorta and began just inferior to the medial side of the entrance of the superior vena cava into the right atrium From this point the margin extended anteriorly and inferiorly to terminate in the fibrous trigone posterior to the membranous ventricular septum The trabeculated right atrial appendage was separated from the anterior margin of the atrial septum by a strip of smooth muscular wall that was loosely adherent to the ascending aorta

The posterior margin extended from the tip of the blade through a convex curvature posterior to the fossa ovalis terminating at the os of the coronary sinus (Figs 1 and 2) The entrance of the inferior vena cava was separated from the posterior margin of the septum by a narrow expanse of free wall of the right atrium

The short inferior margin extended from the os of the coronary sinus to the fibrous trigone posterior to the membranous ventricular septum At no point did it coincide with the tricuspid annulus The tissue between the inferior margin and the tricuspid annulus consisted of right atrial endocardium overlying the interventricular septum

The round to oval shaped fossa ovalis was located midway between the tip of the blade and the inferior margin (Figs 1 and 2) The fossa ovalis was separated from the anterior margin of

Table I Measurements of normal atrial septa means and (ranges)

	Infants (8)	*Children (18)*	*Adults (64)*
Total atrial septal area (mm²)	142 (92 187)	274 (177 445)	890 (450-154[illegible])
Fossa ovalis area (mm²)			
Group A	43 (15 84)	64 (37 111)	240 (97-490)
Group B	—	47 (32-61)	146 ([illegible]9-4[illegible])
Area ratios FO/AS			
Group A	30% (11 48%)	26% (13 40%)	28% (14-46%)
Group B	—	16% (7 23%)	15% (3-[illegible]9%)
Atrial septal width mm	11 (8 13)	14 (10-21)	24 (15-34)
Anterior isthmus width mm	2 1 (1 5 2 5)	3 6 (1 5 7 0)	5 0 ([illegible] 13)
Posterior isthmus width mm	—	3 9 (2 8)	6 1 (2 11)

Group A Hearts with no septal isthmus posterior to fossa ovalis eight infants 14 children and 31 adults.
Group B Hearts with septal isthmus posterior to fossa ovalis four children and 33 adults

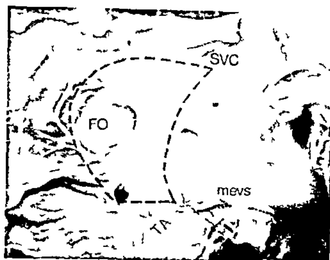


Fig 2 Right atrial view of normal atrial septum *(dashed line)* TA tricuspid annulus Other abbreviations as in *Fig 1*

the septum by a narrow isthmus of septal musculature averaging 2 1 mm in width in infants 3 6 mm in children and 5 0 mm in adults (Table I) Since the anteroposterior width of the atrial septum at this point averaged 11 mm in infants 14 mm in children and 24 mm in adults the anterior isthmus represented only 19 per cent 26 per cent and 21 per cent respectively of the total septal width (Table I)

In one third of the specimens (four children and 33 adults) septal muscle was also present posterior to the fossa (posterior isthmus) When present the posterior isthmus was about the same width as the anterior isthmus (Fig 1) averaging 3 9 mm in children (28 per cent of the total atrial septal width) and 6 1 mm in adults (25 per cent of the total atrial septal width Table I) The posterior isthmus blended smoothly with the fossa ovalis so that the separation between the two was often detectable only by transillumination of the membranous fossa ovalis

The anterior isthmus formed part of the anterosuperior border between the septum and fossa ovalis designated in this study as the limbus (Fig 1) In 70 of the 90 specimens (eight infants, 16 children and 46 adults) the limbus was quite distinct because the septum primum was adherent to the left side of the limbus and the rim of the limbus was as thick as the atrial septum superior to it * (Table I) Patency into the left atrium between the valve of the fossa ovalis and the limbus could be detected only by probing In 20 older specimens (two children and 18 adults) the septum primum was adherent at the center of the limbus The limbus in turn was thinner than the atrial septum superior to it so that there was a gradual transition from fossa ovalis to limbus

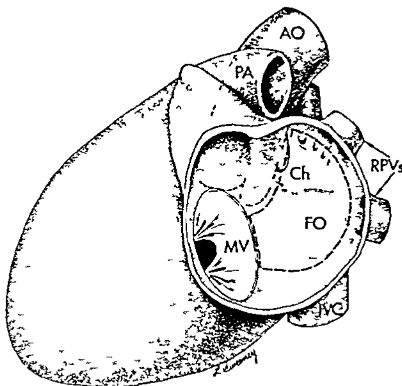


Fig 3 Left atrial view of normal atrial septum *(heavy broken line)* *Dotted line* outlines fossa ovalis *light broken line* outlines margins of ascending aorta and persistent channel *(Ch)* of foramen ovale MV mitral valve Other abbreviations as in *Fig 1*

tissue [6] In six adult hearts this transition was so gradual that the margin between limbus and fossa ovalis was detectable only with transillumination

The area of the atrial septum averaged 142 mm² in infants 274 mm² in children and 890 mm² in adults (Table I) The fossa ovalis was an average of 43 mm² in infants 64 mm² in children and 240 mm in the 53 adult hearts in which there was no septal isthmus posterior to the fossa ovalis (Table I) The area of the fossa ovalis therefore was 30 per cent 26 per cent and 28 per cent respectively of the total area of the atrial septum in the eight infants 14 children and 34 adults In those hearts with an isthmus of septum posterior to the fossa ovalis the area of the fossa ovalis was less averaging 47 mm in children (16 per cent of the total atrial septal area) and 146 mm in adults (15 per cent of the total atrial septal area Table I)

When viewed from the left atrium the anterior margin followed the curvature of the posterior wall of the ascending aorta (Figs 3 and 4) As in the right atrium a wide expanse of smooth free atrial wall muscle separated the anterior margin from the left atrial appendage The posterior margin formed a curve just medial to the entrance of the right pulmonary veins The superior pulmonary vein entered close to the point of the blade The inferior margin on the left side was formed by the mitral annulus The outlines of the fossa ovalis and limbus were not discernible when viewed from the left side except by transillumination

A prominent feature of the left side of the atrial septum was a network of muscular trabeculations formed by remnants of the septum primum The largest of these was a crescentic muscular arch along the anterior border representing the remnant of the ostium secundum[17, 20, 21] Several smaller arches fanned out along the posterior margin of the septum (Figs 3 and 4) In 90 per cent of the hearts (80 specimens) the largest arch marked the entrance to a channel which extended posteriorly to the limbus of the fossa ovalis between the valve of the foramen ovale and the limbic portion of the muscular septum In three hearts one of the smaller arches also communicated with the channel

In 38 of the 80 specimens the channel was patent at the limbus creating a patent foramen ovale This was the case in seven of eight infants



Fig 4 Left atrial view of normal atrial septum *(dashed line)* *MA* mitral annulus Other abbreviations as in *Figs 1 or 3*

(88 per cent) in 11 of 18 children (61 per cent) and in 20 of 64 adult specimens (31 per cent) In the remaining specimens the channel was fused at the limbus by a fragile line of adhesion that was easily broken by gently probing with the rest of the channel being patent for the entire distance between the arch of the ostium secundum and the limbus

In four adult hearts small blind pockets originating from the right side of the limbus abutted these channels but did not communicate with them In these cases the fragile line of adhesion was one or two mm anterior to the crest of the limbus on the left side

In 10 of the 90 hearts (four children and eight adults) the channel was completely obliterated In eight of these hearts a raised lip of tissue along the anterior margin of the septum marked the position of the remnant of the ostium secundum

Discussion

Description of specialized atrial conduction tissue would be of more practical value to the cardiologist or surgeon if related to the clearly defined boundaries of the atrial septum and fossa ovalis The boundaries described in this study provide a tool for localizing this conduction tissue Descriptions *of the anterior and middle* internodal tracts[9] have not attempted to relate their positions to the fossa ovalis or anterior margin of the septum The narrowness of the anterior septal isthmus documented in this study demonstrates that these two tracts must be within *several mm of the limbus at this point* but further work is needed to determine their precise position here and in the superior part of the septum Further the positions of the three internodal conduction tracts in the inferior part of the septum as they converge in the atrioventricular node[9, 13] are important to determine in light of the great distance between the inferior margin of the septum and the tricuspid annulus documented by *this study*

The atrial septal area measurements presented in this study suggest that estimates of the size of atrial septal defects created by balloon septostomy may be too high Defects at least 12 mm in diameter (or 113 mm in area) were reported necessary for good mixing in transposition of the great arteries without ventricular septal defect as measured during balloon septostomy of the fossa ovalis[8] This is twice the area of the average fossa ovalis of either infants or children measured in this study (43 and 64 mm respectively) and is larger than the largest fossa ovalis of any infant or child (Table I) Shrinkage due to fixation could only account for a fraction of this discrepancy as shown by the maximum shrinkage of 23 per cent *in pig hearts examined in* this study The large measurements of fossa ovalis diameter at atrial septostomy may well have represented considerable stretching of the limbus of the fossa ovalis since the measurements were made by pulling the balloon catheter tightly against *the left side* of the septum and progressively deflating the catheter *until it popped back into* the right atrium[1] Since mixing capacity created by balloon septostomy may not be as extensive as presumed from such clinical investigations this study points up the need for correlation of clinical data with anatomic measurements

The persistence of a channel between the fossa *ovalis and muscular* septum in hearts without patent foramen ovale could have clinical importance A channel has been described previously but not the fact that it persists in nearly *all hearts* whether or not a patent foramen ovale is present nor the fact that the *channel always* extends to the edge of the limbus resulting in only a tenuous attachment there Why does the valve of the

foramen ovale become adherent to the muscular septum only at the edge of the limbus? One possibility is that after the normal infant circulation is established and the fossa has functionally closed blood directed from the inferior vena cava at the limbus causes sufficient disruption of the adjacent endothelial surfaces to promote fusion at this point The same disruption does not occur between the valve of the foramen ovale and the septum on the left side This previously unreported tenuous attachment of fossa ovalis to limbus could be the anatomical basis for the ease with which some cardiologists can cross the atrial septum with a blunt catheter in hearts without patent foramen ovale[25] as well as for the development of right to left shunts in individuals with elevated right atrial pressure

Summary

The atrial septum is a blade shaped structure with a concave anterior margin that reflects the curve of the ascending aorta a convex posterior margin and an inferior margin along the mitral annulus The fossa ovalis comprises an average of 28 per cent of the total septal area or 43 mm ^{2} in infants and 240 mm in adults The channel that persists between the fossa ovalis and the muscular atrial septum is patent except at the limbus providing a useful explanation for the success of blunt transseptal atrial catheterization and right to left shunts in individuals with elevated right atrial pressure

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Reduction in ventricular endocardial and epicardial potentials during acute increments in left ventricular dimensions

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The observation that a reduction in right ventricular endocardial potentials occur in patients with acute myocardial infarction or massive pulmonary embolism clinical situations likely to be associated with acute ventricular dilatation indicates that a relationship might exist between the magnitude of ventricular potentials and ventricular volumes [1] Recently it was demonstrated in an experimental study that potentials recorded from the endocardial surface of the left and right ventricles decreased markedly when left ventricular volume was increased by blood transfusion [3] Preliminary data suggested that potentials recorded from the epicardial surface also decreased during volume expansion However the influence of changes in ventricular volumes on endo and epicardial potentials recorded simultaneously from the same site has not been analyzed

The ventricular excitation propagates from the endocardial side with predominantly radial components whereas the propagation is more tangentially oriented in outer epicardial layers [4,5] Analysis of spatial surface electrocardiograms have indicated opposite effects of changes in the intracavitary blood mass and volume on radial and tangential components of the QRS complex [4] Our preliminary observations however indicated directionally similar changes in endocardial and epicardial potentials during acute changes in ventricular volumes Thus the relationship between changes in endocardial and epicardial potentials during acute changes in ventricular volume is not totally clear The present study was, therefore undertaken to clarify the relationship between epicardial and endocardial potentials during acute variations in left ventricular diameter and therefore left ventricular volume

Methods

Experimental preparation Twelve mongrel dogs weighing 16 to 25 kilograms were anesthetized initially with sodium thiopental (25 mg /kg intravenously) Morphine sulfate (45 mg intravenously) was then given and anesthesia was maintained throughout the experiments with regular injections of 15 mg /hr For muscle relaxation a continuous infusion of succinyl choline chloride (20 mg /Kg /hr) was given The dogs were intubated and ventilated with a positive pressure respirator (Harvard Apparatus Millis Mass) respiration was adjusted under the guidance of frequent analyses of arterial blood pH pO and pCO_2 (BMS MK2 Radiometer Copenhagen)

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The chest was opened by mid sternotomy and the pericardium was opened and retracted The right atrium was paced in nine of the 12 dogs with an electrode attached to the atrial appendage (Grass Instruments Quincy Mass)

Electrical measurements Potentials from the endocardial surface of the left and right ventricles (Endo Pot) were recorded with thin wire hook electrodes with a diameter of 0 13 mm (Elgiloy Elgiloy Corp Elgin Ill) on an electrocardio graph (Honeywell San Jose Ca) The entire length of the wire except the distal 4 mm was insulated The electrodes were mounted in 23 gauge needles and were introduced into the ventricular cavities upon withdrawal of the needle the electrode hook sank approximately 2 mm into the endocardial tissue layer Initially a contact pattern of ST segment elevation was regularly observed but after one hour the ST segment elevation was markedly reduced Elec trodes showing persistent ST segment elevation greater than 2 mV after one hour were discarded from subsequent analysis

Potentials from the epicardial surface (Epi Pot) were recorded with a cotton wick electrode with an area of 5 mm The epicardial sites were defined according to anatomical landmarks so that they corresponded to the underlying endo cardial wire electrodes A total of 32 pairs of endocardial and epicardial electrodes were used for recording left ventricular endo and epicardial potentials respectively In five dogs one electrode was placed through the right ventricular cavity into an endocardial position on the left side of the interventricular septum In four dogs right ventricular endocardial potentials were also recorded from the free wall (endocardial surface) of the right ventricle In three of the dogs wire electrodes were also inserted in an epicardial position and the Epi Pot recorded with wire electrodes could be compared with the potentials recorded with wick electrodes at the same epicar dial sites The correlation of 158 paired ob erva tions at eight different sites with the two methods was

$$\text{Wick Pot} = 0\,93\ \text{Wire Pot} + 0\,47$$

The regression coefficient was $r = 0\,972$ and the regression line was not statistically different from the line of identity

The Wilson central terminal of extremity leads was used as reference for all electrograms Signals below 0 5 Hz and above 100 Hz were excluded by bandpass filters Potentials were accepted fo analysis provided correct endocardial electrod positions were verified by postmortem examina tion of the heart and only the potentials recorde from such satisfactory electrode positioning wer analyzed The amplitude of QRS complexes fron four consecutive beats were averaged an regarded as endo or epicardial potentials Ectop beats or QRS complexes revealing conductio disturbances were excluded The potentials wer integrated over time by analog computer (Elec tronics Assoc Inc West Long Branch Ne Jersey) giving the area of the QRS comple (mV msec) above the isoelectric T P segmen for each beat The integrator was triggered an reset by the left ventricular pressure signals an appropriate delay controls

Hemodynamic measurements Left ventricu lar diameter was continuously recorded by th ultrasound time between two piezoelectric crys tals inserted into the anterior and posterior wall of the left ventricle[4] Left ventricular pressur was measured with a solid state transducer (Kon igsberg Instruments Pasadena Ca) inserte from the left atrial appendage Aortic pressur was measured through a femoral cathete connected to a Statham P23Db transducer an aortic flow was measured with an electromagnet ic flowmeter (Carolina Medical Electronics King No Carolina) on the ascending aorta

Experimental procedure Control measure ments of potentials and hemodynamic parame ters were performed when the initial electrocar diogram contact pattern had disappeared Homo logous and prewarmed blood was then infuse into the jugular vein through a wide bore cathe ter for stepwise increase in left ventricular end diastolic diameter (LVEDD) and pressur (LVEDP) For each step the infusion rate wa slowed down to maintain stable hemodynamics and measurement of potentials and hemody namic parameters were repeated Infusion wa continued until LVEDP had reached 15 to 2 mm Hg infused blood volume was 550 to 2 50 ml Thereafter blood was withdrawn stepwise t allow LVEDD and LVEDP to return to control The above procedure allowed us to treat th recorded potentials as a regression problem fo each electrode separately with respect to th changes in LVEDD during infusion and with drawal of blood Table I gives the control value and the values obtained at the highest LVED

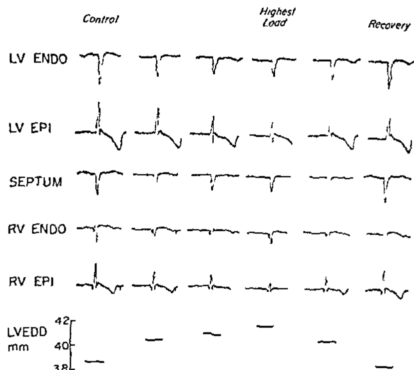


Fig 1 Potentials recorded from the left *(LV)* and right *(RV)* ventricles with the interventricular septum during stepwise infusion and withdrawal of blood Potentials were recorded at corresponding endocardial *(ENDO)* and epicardial *(EPI)* sites of the ventricular walls *LVEDD* = left ventricular end-diastolic diameter

achieved where each dog and electrode served as its own control

Student s t test for paired data was applied in calculating statistical probability * A p value less than 0 05 was regarded as statistically significant As similar relationships between Endo Pot and Epi Pot and LVEDD were observed in paced and non paced hearts the data were therefore pooled for final analysis

Results

Fig 1 shows changes in potentials recorded from the left and right ventricular endo and epicardium and from the interventricular septum in one experiment The potentials from both endo and epicardial surfaces decreased as LVEDD was increased stepwise during blood transfusion When LVEDD returned to control after withdrawal of blood the potentials increased and also returned to control values The absolute magnitude of the potentials recorded either from endocardium or epicardium of the left or right ventricle varied considerably according to electrode site and also position in different dogs ranging from 17 to 51 mV (see Fig 2) However irrespective of the recording site and the initial magnitude linear reduction in potential was observed for each individual electrode as LVEDD was increased Both endocardial and epicardial potentials recorded from either ventricle and also potentials from the interventricular septum behaved similarly Table I summarizes changes in potentials and hemodynamic parameters during maximum volume load achieved On the average LVEDD increased by 11 per cent from 39 41 ± 1 72 to 43 60 ± 1 89 mm Similarly LVEDP increased from 4 9 ± 1 0 to 17 3 ± [illegible] mm Hg Blood transfusion caused an increase as expected in cardiac output and the systolic blood pressures

To assess the magnitude of changes in endo and epicardial potentials recorded from the same area of the ventricular wall the ratio of Endo/Epi potentials was calculated for each pair of endocardial and epicardial electrodes separately At control LVEDD of 100 per cent the ratio of Endo/Epi potentials recorded from the left ventricle averaged 1 04 ± 0 04 and at LVEDD of 111 per cent this ratio decreased to 0 72 ± 0 06 suggesting a relatively greater reduction in left ventricular endocardial potential than in its counterpart, epicardial potential Statistical

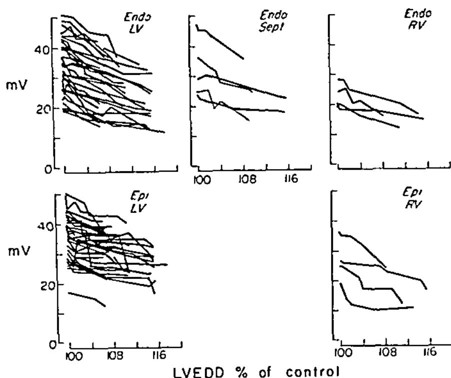


Fig 2 Relationship between cardiac potentials and left ventricular diameter during blood infusion One line for each electrode Abbreviations = the same as those in *Fig 1*

analysis of the individual regression lines of the ratios of left ventricular Endo/Epi potentials revealed that the ratio was significantly reduced by volume loading (Slope = 0 016 ± 0 002 $p < 0\,001$) Such changes however were not observed in the ratios of right ventricular endo and epicardial potentials

Endo pot recorded from the left ventricular septum behaved similarly to Endo Pot recorded from the endocardium of the left ventricular free wall (Table I)

The area of the QRS complexes similar to its absolute magnitude showed a linear reduction with increasing diameter of the left ventricle Duration of the QRS complex did not change suggesting lack of conduction disturbances (average 42 9 ± 0 3 msec) An apparently greater reduction in epicardial QRS area compared to the reduction in Epi Pot could be accounted for by the fact that the integrator substracted small negative areas below the isoelectric base line (Fig 1)

Discussion

The present study was designated to investigate the influence of acute changes in ventricular volume on concurrently recorded right and left ventricular endo and epicardial potentials The findings indicate that acute changes in left ventricular diameters markedly influence not only the magnitude of the right or left ventricular endocardial potentials as previously reported[3] but also of their epicardial potentials Thus an increase in left ventricular diameter during blood transfusion was accompanied by a decrease in both endo and epicardial potentials recorded either from the right or the left ventricle With an 11 per cent average increase in left ventricular end diastolic diameter there was a 15 per cent decrease in left ventricular epicardial and 37 per cent decrease in right ventricular epicardial potentials As observed in previous investigations both left ventricular endocardial (−27 per cent) and right ventricular endocardial (−36 per cent) potentials also decreased concurrently

The precise mechanism of such changes in ventricular potentials with changes in ventricular diameter is not clear That changes in ventricular geometry and wall thickness may contribute needs to be considered A considerable decrease in thickening of ventricular walls may occur during acute expansion of ventricular volume During

Table 1 Effect of blood infusion on cardiac potentials (Mean ± SEM in twelve dogs)

	N	Control	Highest load	P
Left ventricle				
Endo Pot mV	33	33.1 ± 1.8	23.9 ± 1.6	0.001
Area mV msec	33	622 ± 43	508 ± 42	0.001
Epi Pot mV	33	34.7 ± 1.3	29.6 ± 1.2	0.001
Area mV msec	33	281 ± 35	219 ± 32	0.01
Interventricular septum				
Sept Pot, mV	5	31.8 ± 4.4	23.0 ± 3.4	0.002
Area mV msec	5	568 ± 124	431 ± 99	0.05
Right ventricle				
Endo Pot mV	4	22.8 ± 2.1	14.5 ± 0.9	0.01
Area mV msec	4	264 ± 81	205 ± 61	NS
Epi Pot mV	4	27.0 ± 3.5	17.0 ± 3.2	0.01
Area mV msec	4	222 ± 28	106 ± 34	0.05
Hemodynamic parameters				
LVEDD mm	12	39.41 ± 1.72	43.60 ± 1.89	0.001
LVEDP mm Hg	12	4.9 ± 1.0	17.3 ± 2.1	0.001
LVSP mm Hg	12	129 ± 6	155 ± 7	0.001
HR beats/min †	12	164 ± 6	159 ± 7	NS
CO ml/min	5	3730 ± 120	5420 ± 800	0.05

Endo Pot = endocardial potential Epi Pot = epicardial potential Sept Pot = interventricular septal potential Area = integrated area of QRS complex above the isoelectric T P segment LVEDD = left ventricular end-diastolic diameter LVEDP = left ventricular end diastolic pressure LVSP = left ventricular systolic pressure HR = heart rate CO = cardiac output N = number of observations P = probability value NS = not significant
†Atrial pacing in nine dogs.

such thinning of the ventricular wall the tissue mass in the immediate vicinity of the recording electrode that delivers the electrical signals is reduced This might account for reduction of both endo and epicardial potentials during volume expansion In the present study decrease in left ventricular endocardial potentials was of greater magnitude than that of corresponding epicardial potentials That such a difference in changes in left ventricular endo and epicardial potentials was observed also supports the hypothesis that thinning of the left ventricular free wall may be at least partly responsible for reduction in ventricular potentials during an increase in ventricular volume During volume expansion subendocardial layers will be expected to be stretched more than the subepicardial layers The diameter crystals in the experiments in the present study were placed in mid wall position Assuming a spherical and symmetrical left ventricle with a wall thickness of 12 mm before volume expansion it can be calculated from the changes in left ventricular end diastolic diameter (Table I) that the inner endocardial diameter increased by 51 per cent during blood transfusion whereas the outer epicardial surface increased only by 8 per cent The actual increase in the diameter of subendocardial layers could have been less than expected because of the presence of wrinkling and trabeculations However, it is most likely that the subendocardial layers will be more stretched and thinned than the subepicardial layers of the left ventricular wall during volume expansion The absence of a significant difference in the changes of endocardial and epicardial potentials, when recorded from the right ventricular free wall can also be explained by the fact that the right ventricular free wall is much thinner Therefore a much smaller difference in the increased diameter of endocardial and epicardial layers of right ventricular free wall would be expected during volume expansion

Studies of body surface potentials and simulator experiments have suggested that the increase in intracavitary blood volume a highly conductive mass augments the radial components and decreases the tangential components of ventricular excitation potentials[6, 7, 10, 11] A radial propagation of ventricular excitation is dominant in endocardial layers, whereas the epicardial propagation is much more tangentially oriented[4, 5] If such mechanisms was operative in the present study, divergent changes between endo and epicardial potentials would be expected during volume expansion by blood transfusion Such discordant changes however were not detected in the present study as both endo and epicardial potentials decreased during an increase in ventricular diameter These findings imply that potentials recorded directly from endo and epicardial surfaces cannot be compared to spatial surface vectorcardiograms Our findings are in agreement with the observations of Angelakos and Gokhan [2] who also reported that changes in epicardial and body surface potentials were different during vena caval obstruction which presumably caused an alteration in ventricular volume Surface potentials reflect the total cardiac electri

cal activity as a result of vastly complex propagation patterns of potentials throughout the body[13] whereas a unipolar electrode placed directly in cardiac tissue most likely will reflect predominantly the electrical events in the surrounding myocardial tissue

Changes in hematocrit have been shown to influence surface potentials[14, 15] Marked reduction in hematocrit to below 35% might reduce endocardial potential[3] However only minor changes in hematocrit (38 to 44 per cent) occurred during transfusion of whole blood in these experiments and reduction in endocardial and epicardial potentials were clearly seen even in those experiments where the hematocrit increased slightly during blood transfusion Hemolysis was observed in some of the experiments and it might be argued that increased plasma concentrations of potassium from hemolysis might have increased conductance accounting for changes in potentials This is however unlikely because following withdrawal of transfused blood control values of cardiac potentials were almost always regained as the left ventricular end diastolic diameter also returned to control

It has recently been suggested that reduction of the R wave amplitude of the epicardial QRS complex may indicate enhancement of myocardial ischemic injury following coronary artery ligation[16] Such a decrease in R wave amplitude however may be related to increase in left ventricular volume which is consistently observed during experimental myocardial infarction The development of Q waves and reduction of R wave magnitude after infarction might however also be influenced by the relationship described here between epicardial potentials and left ventricular dimensions Ventricular dilation is a consequence of acute myocardial ischemia[1] and it is possible that this is reflected in reduced QRS voltage in epicardial leads from all parts of the left ventricle The same argument also applies to the interpretation of changes in QRS voltage to assess the effect on the ischemic injury of interventions that simultaneously alter left ventricular dimensions It should be emphasized however that our measurements of the relationship between cardiac potentials and ventricular dimensions were performed in acute experiments and that the long term relationship remains unknown

Although in the present study the absolute magnitude of potentials endocardial and epicardial varied considerably according to the electrode sites a strong negative correlation existed between changes in left ventricular diameter and endo or epicardial potentials recorded from each site whether from the right or the left ventricle These findings strongly suggest that monitoring of right ventricular endocardial potentials may be useful clinically to detect acute change in ventricular volume

Summary

Unipolar potentials were recorded from the endocardium (Endo Pot) and the epicardium (Epi Pot) of the left and right ventricles of anesthetized open chested dogs during acute changes in left ventricular dimension by blood transfusion A pair of implanted ultrasonic crystals were used to detail changes in left ventricular (LV) anteroposterior diameter When the diameter increased by an average of 11 per cent LV Endo Pot decreased by 28 per cent and LV Epi Pot decreased by 15 per cent Right ventricular Endo Pot and Epi Pot concurrently decreased by similar magnitude (−36 per cent) The relationship between potentials and LV diameter showed negative linearity over the ranges examined and was not influenced by changes in hematocrit No inverse relation between changes in Endo Pot and Epi Pot was observed It is suggested that potentials when recorded directly from the endocardium or epicardium mainly reflect the electrical activity of the tissues in the immediate vicinity of the electrode It is postulated that an increase in ventricular volume by producing stretching and thinning of ventricular walls reduces the effective tissue mass represented in the electrode signal thereby accounting for a reduction in both endo and epicardial potentials Although the precise mechanism of changes in ventricular potentials remains unclear such changes nevertheless may indicate in clinical circumstances an acute shift in left ventricular volume

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Contour graph for relatıng per cent success ın achıevıng ventrıcular defıbrıllatıon to duratıon current, and energy content of shock

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There is considerable controversy concerning the waveform and energy requirements for the successful transthoracic ventricular defibrillation of large and very large patients[1,2] For animal data to be of maximum value in helping resolve this controversy the presentation of such data should be in a concise and easily interpretable form

Geddes and colleagues have presented much of their experimental defibrillation data in the form of strength-duration curves in which threshold values of current energy and charge required to achieve ventricular defibrillation are plotted as functions of the duration of the applied pulse For studies with electrodes directly on the heart the various strength variables are normalized by dividing the actual values by the weight of the heart for studies conducted on a transthoracic basis normalization involves division by body weight

Conventional strength-duration curves are widely used in the presentation of physiological data involving thresholds Although instructive and effectual in many respects such curves do have certain limitations when used to display defibrillation data in which there is considerable variation in response from episode to episode in a given animal and from one animal to another Under such conditions the concept of a threshold becomes blurred and consequently the strength-duration curve loses some significance Furthermore strength-duration curves are usually considered to relate the variables in such a way that strength is a single valued function of duration with an increase in strength at any given duration eliciting a response as the strength-duration curve is crossed No provisions are ordinarily made for the possibility that strength may be a double valued function of duration with an increase in strength sometimes causing a decrease in desired response Yet such a situation can occur in ventricular defibrillation

We have presented much of our own experimental defibrillation data in the form of multicurve graphs Each curve in a graph represents a given value of current and per cent success in achieving ventricular defibrillation is then plotted as a function of duration energy content or charge content of the applied pulse[6,7] In this method of displaying defibrillation data the concept of a threshold for response is replaced by more explicit criteria in which per cent success figures are associated with given stimuli While furnishing more information than strength-duration curves the method which we have used for presenting data does not highlight the interrelationship between for example the current amplitude and the duration of pulse which exists for a given per cent success level as well as if the data

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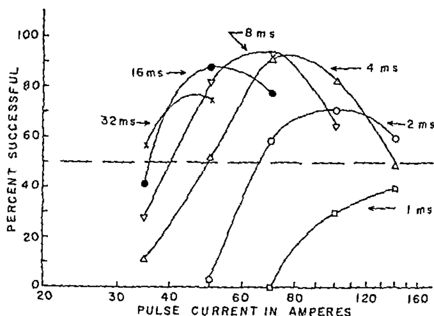


Fig 1 Relationship between per cent success in achieving transthoracic ventricular defibrillation in 100 kilogram calves and the amplitude of the current of rectangular wave shocks

were plotted on the duration-current amplitude plane used with strength-duration curves

In the present paper we draw from both kinds of data presentations and expand upon an approach involving contour graphs [13] which was initially conceived by A M Dolan in 1966 when he was a graduate student working with our group to develop an improved method for displaying defibrillation data

Methods

Our procedures for transforming data for use in contour graphs can best be explained by reference to data associated with a specific experimental study In an investigation involving transthoracic ventricular defibrillation in calves weighing 90 through 110 kilograms (mean of 100 kilograms) with rectangular wave shocks the per cent success in achieving first shock defibrillation with waveforms having amplitudes of 35 50 70 100 and 140 amperes and durations of 0 5 through 64 msec was evaluated [1] From the tabulated results of the study a family of curves (one curve for each of the five current amplitudes) of per cent successful defibrillation versus pulse duration was drawn This family of curves appears in the paper cited From the same data base curves of per cent success versus pulse current for pulse durations of 1 2 4 8 16 and 32 msec can be plotted This family of curves is shown in Fig 1 The intersections of horizontal lines drawn at the 25 50 70 80 and 90 per cent success levels with the individual curves in these two families of curves determine 51 pairs of pulse duration-pulse current values for plotting on the contour graph One such horizontal line drawn at the 50 per cent success level is shown in Fig 1

Data for plotting isoenergy curves on the pulse duration-pulse current plane are obtained in a manner which parallels the method used for obtaining data for plotting the equi per cent success contours From the tabulated results of our calf study [12] families of curves of the energy content of the pulse versus pulse duration (one curve for each of the five current levels) and of energy content versus pulse current (one curve each for pulse durations of 1 2 4 8 16 and 32 msec) are drawn The intersection of horizontal lines drawn at the 100 200 400 800 and 1600 joule levels with the individual curves in these two families of curves determine 41 pairs of pulse duration-pulse current values for plotting on the contour graph When plotted on log log coordinates the points determined by these pairs of values lie to a good approximation along five straight lines which are then drawn using analytical least squares techniques

Making use of extensive experimental data in two earlier papers [10, 11] the procedure for determining the equi per cent success curves for the contour graph for medium sized dogs was similar to the procedure described above Since our earlier

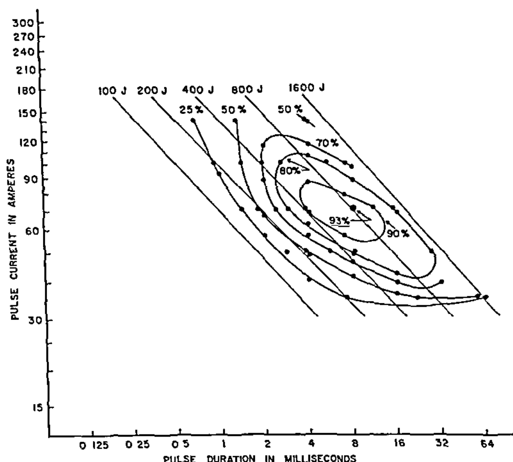


Fig. 2. Contour graph relating per cent success in achieving transthoracic ventricular defibrillation in 100 kilogram calves to the duration, current, and energy content of rectangular wave shocks.

papers did not report the energy values associated with each of the pulse duration-pulse current combinations studied, the isoenergy lines on the contour graph are based upon a chest resistance of 60 ohms—a typical value observed in the experiments and used in the derivation of the per cent success versus energy graphs in the two papers.

In using contour graphs for comparing transthoracic defibrillation data from different species, minimizing or eliminating the influence of weight or size difference per se is desirable. On a theoretical basis and utilizing an idealized model, we have shown that if the instantaneous current density vector at corresponding points within the myocardium (and thus also presumably the per cent success in achieving defibrillation) in animals of the same species remains invariant with weight, then the electrode diameter, the instantaneous current, the delivered energy, and the chest resistance are proportional to the one third, two thirds, first, and negative one third power, respectively, of body weight.[1] If, as in a previous paper,[1] an average weight of 19.23 kilograms is assumed for the dogs, our actual dog data, as shown, for example, on a contour graph, can be transformed to apply to a hypothetical 100 kilogram dog by using a weight ratio of 100/19.23 = 5.2. The current scale is then multiplied by $(5.2)^{2/3}$ = 3 and the energy notations are multiplied by $(5.2)^{1}$ = 5.2. In this transformation, pulse duration and, of course, per cent success entries remain unchanged.

Results

A contour graph for 100 kilogram calves derived as outlined above is shown in Fig. 2. The large dot at 8 msec. and 70 amperes designates the most effective waveform *(93 per cent successful)* in the data base from which the contour graph was derived. Logarithmic scales are used for both pulse duration and pulse current. The numbering

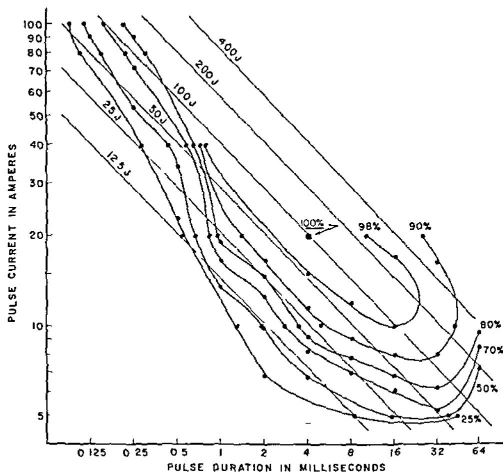


Fig 3 Contour graph relating per cent success in achieving transthoracic ventricular defibrillation in medium sized dogs to the duration current and energy content of rectangular wave shocks

sequence associated with the pulse current scale simplifies the comparison of data in the contour graph with data displayed in the contour graphs for the dog To minimize clutter points used in the derivation of the isoenergy lines are not shown on the graph Reflecting a complex variation of chest resistance with pulse duration and pulse current the isoenergy lines in Fig 2 have slopes which differ slightly from the value associated with a constant value of chest resistance and which vary somewhat from line to line As a consequence these lines are not exactly parallel

A contour graph for medium sized dogs is shown in Fig 3 The large dot at 4 msec and 20 amperes designates the most effective waveform *(100 per cent successful)* in the data base from which the contour graph was derived As in Fig 2 contours are drawn at the 25 50 70 80 and 90 per cent success levels In addition and because the data indicate that higher per cent success levels are achievable in the dog a contour line is drawn at the 98 per cent success level Based upon assumed constant value of chest resistance isoenergy lines in Fig 3 are parallel and equa spaced

While the direct transformation of the cont graph of Fig 3 to apply to a hypothetical kilogram dog would yield a current scale wh would be identical to the scale used for our cal the numerical values of the transformed isoen gy lines would differ from those shown in Fig Consequently in making the transformati from Fig 3 to Fig 4 the isoenergy lines were n transformed Instead on the contour graph Fig 4 new isoenergy lines were drawn corr sponding to the energy levels used in Fig Th new isoenergy lines are based on a transform chest resistance of 60 × (5 2) ≈ 34 6 ohms

Discussion

The information contained in Figs 2 3 and 4 unusually easy to acquire and interpret particular value is that the contour graphs allo

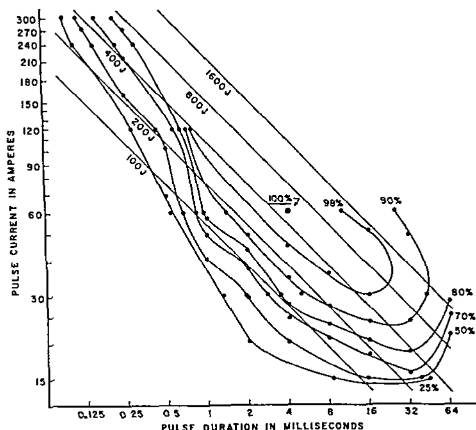


Fig 4 Contour graph relating per cent success in achieving transthoracic ventricular defibrillation in a hypothetical 100 kilogram dog to the duration current and energy content of rectangular wave shocks

one to quickly grasp the interrelationships which exist among the four variables and to critically compare defibrillation data from different species

For example from the closed 90 per cent success level contour curve in Fig 2 which appears to be centered at about the 7 5 msec -68 ampere-700 joule point the combinations of values of pulse duration current and energy which will yield effective defibrillation in the 100 kilogram calf (in the 90 to 93 per cent success range) are immediately apparent The nature of the near tangential intersection of the 200 joule isoenergy line with the 50 per cent success contour indicates that defibrillation at the 50 per cent success level in 100 kilogram calves can be realized with 200 joule shocks over only a rather limited range of duration and current values

Although the data from which the 98 per cent success level contour line in Fig 4 was derived were not sufficient to allow plotting a completely closed curve from the portion of the curve which is plotted the contour curve might be visualized as being centered at about the 5 msec -60 ampere-625 joule point Subject to some uncertainty about the shape of the missing portion of the curve very effective defibrillation in the hypothetical 100 kilogram dog (in the 98 to 100 per cent range) should be realizable over a very wide range of values of duration current and energy Furthermore the nature of the intersection of the 100 joule isoenergy line with the 50 per cent success level contour curve indicates that with 100 joules of energy achieving defibrillation in more than 50 per cent of the episodes over a wide range of values of duration and current can be anticipated It is significant we believe that data concerning successful defibrillation at low and moderate energy levels in large human patients which has been reported by Pantridge and colleagues by Crampton and Hunter[4] by Anderson and Suelzer[5] by Cherwek and colleagues[6] and by Campbell and co workers appear compatible with those shown in Fig 4

In comparing the contour graphs of Figs 2 and 4 one immediately notices that although the

apparent centers of the highest per cent success level contours fall at energy levels which are not too different the contours for the hypothetical 100 kilogram dog are spread out much more than are the corresponding contours for the 100 kilo gram calf Because of this difference the specifi cations for an effective defibrillatory shock in the hypothetical 100 kilogram dog are much less critical than for the calf

In a formal manner and to the extent that our theoretical size scaling procedure is valid [14] Figs 2 and 4 may be modified to apply to any other body weight m by multiplying each of the indicated current values by $(m/100)^{3/4}$ and multiplying each of the indicated energy values by $(m/100)$ Because logarithmic coordinates are used for both pulse duration and pulse current isocharge curves when plotted on the graphs of Figs 2, 3 and 4 appear as straight parallel lines If initially plotted on the contour graphs of Figs 2 and 4 these isocharge lines are scaled when the graphs are modified to apply to other body weights by multiplying the indicated values by $(m/100)^{3/4}$

The contour graphs in this paper relate per cent success in the initial attempt to terminate an episode of ventricular fibrillation to the parame ters of the shock employed In the defibrillation of humans first shock success is clearly not the only factor to be considered For example when porta bility is of major concern it may well be advan tageous to utilize lower energy shocks which can be generated with smaller and less complex defi brillators Multiple shocks from such apparatus when required can serve to increase appreciably the success rate per episode of fibrillation over the first shock results with the same shock Further study is needed to determine whether the low energy multiple shock strategy is advantageous when portability is not of major importance

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The electrophysiologic effects of intravenous propranolol in the Wolff-Parkinson-White syndrome

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The Wolff Parkinson White (WPW) syndrome[1] is characterized by a shortened PR interval a widened QRS complex and paroxysmal tachy cardia The electrocardiographic pattern denotes early activation (pre excitation) of part of the ventricles via an anomalous or accessory path way which bypasses the main conduction delay in the atrioventricular (AV) node

Since 1930 the syndrome has been of great interest to electrophysiologists because the paroxysmal tachycardia may be explained on a reciprocating or reentry basis utilizing one AV pathway anterogradely and the other retrograde ly It therefore suggested that other tachycardias in patients without the WPW syndrome may be similarly mediated

From the clinical standpoint a major problem has been the discovery of effective drug therapy for use both acutely during an episode of tachy cardia and for long term prophylaxis A large number of drugs alone or in combination have been used with varying success[2 8] Gettes and colleagues[9] hypothesized that propranolol would be the drug of choice in re entry supraventricular tachycardia in patients with or without the WPW syndrome Gallagher and associates[6] and Chung[7 8] also recommended the use of proprano lol in the WPW syndrome It is difficult however to assess the effect of any therapy in the WPW syndrome Patients may overstate or understate the incidence of palpitations[10 13] Furthermore the tachycardias are paroxysmal and may be short lived and so are difficult to document[15 16]

Electrophysiologic studies have been of value in the assessment of drug therapy in the WPW syndrome They have demonstrated that the normal AV pathway and the accessory pathway may respond differently to drugs[17 7] and that significant depression of the AV node by vera pamil[3] for example or of the accessory pathway by amiodarone[24] ajmaline[2] quinidine[7] or procainamide[21 27 25 7] for example may be bene ficial in patients with the WPW syndrome

As regards propranolol however perhaps surprisingly in view of the recommendations for its use limited electrophysiologic data is in fact available[8 6] The purpose of this study is to determine the relevant electrophysiologic effects of intravenous propranolol in the WPW syn drome thereby to provide information concern ing its clinical use

Material

Fourteen patients with the WPW syndrome were studied There were 10 males and four females Eight patients had type A WPW

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Table I Electrophysiologic data—anterograde AV conduction

	Patient		Tachycardia		Sinus rhythm						Atrial pacing				Atrial extrastimulation					
					HR		AVN CT		AP CT		AVN ERP		AP ERP		AVN ERP		AP ERP		AM ERP	
	Sex	Age	Years	Freq	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P
1	M	62	0 5	1+	51	47	100	85			400	400			325	375				
2	F	46	20	2+	90	75	90	120	120	130	250	316	333	333	265	295	285	305		
3	M	19	8	2+	69	56	110	90	90	90			316	316	300	315	340	345		
4	M	49	2	1+	56	52			110	110			333	353	290	295	375	360		
5	M	32	27	3+	80	72			110	110			286	286	280	270	280	[illegible]		
6	F	24	1 3	4+	90	82	90	90	110	110			240	286	265	275	275	290		
7	F	36	4	1+	80	62	100	110	125	135			250	300			235	[illegible]	230	265
8	M	18	0 2	3+	63	54	70	80	80	100	400	400			260	280	445		255	[illegible]
9	F	25	8	2+	78	82	60	125	100	100			273	273			275	275	260	240
10	M	19	5	2+	63	67	110	110	90	110			273	273			285	285	200	200
11	M	48	30	2+	60	55	90	80	110	110			286	316	285	290	305	310	285	255
12	M	62	37	3+	93	97	50	60			261	286			210	270			200	205
13	M	16	5	2+	84	92	95	110	120	110			225	240	235	235	235	240	230	200
14	M	16	9	2+	105	98	95	135	100	115			185	230			205	230	200	205
Mean		34	11	2+	76	71	83	100	105	111	328	350	273	291	272	280	281	290	233	236
± SEM		±4	±3		±4	±5	±5	±6	±4	±4	±42	±29	±14	±11	±10	±10	±14	±12	±11	11
p value					<0 05		NS		NS		NS		0 01		<0 05		NS		NS	

Abbreviations and symbols Tachycardia years = duration of clinical history tachycardia frequency = approximate occurrence daily 4+ weekly 3+ monthly 2+ yearly 1+ HR = heart rate AVN = atrioventricular node AP = accessory pathway AM = atrial muscle CT = conduction time (msec) ERP = effective refractory period (msec) C = control P = propranolol. Statistical evaluation relates only to those cases where measurement was made both in the control state and after propranolol. NS = not significant

syndrome[25] and in three of these the WPW anomaly was intermittent Six patients had type B WPW syndrome[1] The patients ages ranged from 16 to 62 years (mean 34 ± 4 years) Tachycardia had been present for a mean of 11 ± 3 years with a mean frequency of approximately monthly occurrence Only one patient (patient No 1) had associated organic heart disease having suffered an acute inferior myocardial infarction 3 years prior to study (Table I)

Methods

The studies were performed in the fasting state after obtaining informed consent The patients had not received any medication for at least 48 hours prior to the study Intracardiac electrogram recordings were obtained with standard techniques Electrograms were recorded on a multichannel photographic recorder with paper speeds between 25 and 100 mm /sec (Electronics for Medicine Model DR 12) Multiple standard electrocardiographic leads were recorded with high right atrial low right atrial coronary sinus and His bundle electrograms

During sinus rhythm the heart rate and P delta AH and HV intervals were measured High right atrial pacing was performed at increasing rates to assess anterograde AV refractoriness The anterograde AV node effective refractory period was taken as the cycle length of the maximum rate of atrial pacing where 1 1 AV node conduction was preserved The anterograde accessory pathway effective refractory period was taken as the cycle length of the maximum rate of atrial pacing were 1 1 accessory pathway conduction was preserved The atrial extra stimulus technique during atrial pacing was used to determine the anterograde AV node and accessory pathway effective refractory periods and the atrial muscle effective refractory period Right ventricular apical pacing was performed at increasing rates to determine the retrograde ventriculo atrial (VA) conduction time and effective refractory period The VA conduction time was measured from the ventricular stimulus artefact to the onset of the high right atrial electrogram The VA effective refractory period was taken as the cycle length of the maximum rate of ventricular pacing where 1 1 VA conduction was preserved The ventricular extrastimulus technique during ventricu-

Table II Electrophysiologic data—retrograde VA conduction

	Ventricular pacing												*Ventricular extrastimulation*					
					AVN CT				*AP CT*									
	AVN ERP		*AP ERP*		*Min*		*Max*		*Min*		*Max*		*AVN ERP*		*AP ERP*		*VM ERP*	
Pt	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P
1																		
2			300	333					220	225	240	245			255	305	225	
3			300	316					185	180	200	200			235	245	225	230
4			316	353					135	140	160	165			355	365	230	
5			222	261					195	180	250	270			230	240	210	225
6			222	250					140	190	195	200			210	235	205	230
7			261	300					205	200	220	225			225	250	220	230
8	667			667	200		210			235		235	545			650		
9	462	545			255	275	280	280					280	390				
10			250	261					175	175	185	190			240		235	
11			300	316					205	190	250	255			235	245	225	235
12			222						140		200				180	195	175	190
13			205	220					145	180	175	195			205	190	195	185
14			205	220					130	185	210	270			235	185	165	175
Mean			258	283					174	185	209	217			237	246	203	213
± SEM			±14	±15					±11	±7	±10	±10			±15	±17	±8	±9
p value			<0.001						NS		0.005				NS		<0.05	

Abbreviations: VM = ventricular muscle. Other abbreviations as in Table I.

pacing was used to determine the VA effective refractory period and the ventricular muscle effective refractory period.

The initiation by these maneuvers[3,4,5] of re-entry tachycardia and atrial fibrillation or flutter was noted. The cycle length and VA conduction time in the case of re-entry tachycardia and the shortest RR interval of the ventricular response in the case of atrial fibrillation or flutter were measured.

The above procedures were repeated with the catheters in the same positions 15 minutes after termination of an intravenous infusion of propranolol 0.1 mg/Kg at a rate of 1 mg/minute. The electrophysiologic studies were repeated within 15 minutes. Statistical evaluation was performed with Student's t test for paired samples.

Results (Tables I, II, and III)

Sinus rhythm. After propranolol administration there was a decrease in mean heart rate of 7 per cent from 76 ± 4 per minute to 71 ± 5 per minute (p = 0.03). The AH interval or antegrade AV node conduction time was measured in 12 patients. A His deflection could not be seen in two patients being obscured in the delta wave of the His bundle electrogram. The mean AH interval increased by 14 per cent after propranolol from 88 ± 5 msec to 100 ± 6 msec but this was not statistically significant (p = 0.14). The P delta interval, an estimate of the anterograde accessory pathway conduction time, was measured in 12 patients. In two patients delta waves were not present at the time of the study. The mean P delta interval increased by 6 per cent after propranolol from 105 ± 4 msec to 111 ± 4 msec but this was not statistically significant (p = 0.07).

Atrial pacing. 1:1 accessory pathway conduction was absent at all rates during atrial pacing in three patients so that only the AV node effective refractory period could be measured. In an additional patient with increasing rates of atrial pacing 1:1 accessory pathway conduction failed before 1:1 AV node conduction[3,4,32,33] so that both the accessory pathway and the AV node effective refractory periods could be measured. In these four patients second degree block in the normal AV pathway occurred at the level of the AV node. In 10 patients 1:1 accessory pathway conduction was preserved at the maximum rate of atrial pacing with 1:1 AV conduction. In these cases the His deflection could not be readily

Table III Electrophysiologic data—tachycardia initiation

	Reentry tachycardia																Atr fibr…
	AVN AP				AP AVN				AVN AVN				Tachycardia zone				
	CL		R AP CT		CL		R AVN CT		CL		R AVN CT		Duration		Outer limit		AP …
Pt	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
1																	
2	360	420	130	145									0	0	265	295	
3	330	330	175	185									0	0	300	315	
4																	
5	295	355	170	125	280	290	230	240					0	0	285	290	
6	320	345	100	100									0	0	265	2 5	
7	340	395	125	125													240
8									320	330	110	115	60	0	370	280	
9																	
10																	
11		340		135													
12	275	320	115	105	255	280	210	210					190	70	415	310	
13	255	265	140	145									10	0	245	235	180
14					290	300	190	210					50	55	255	285	160
Mean	311	347	136	133	275	290	210	220					39	16	294	286	
± SEM	±14	±19	±10	±11	±10	±6	±12	±10					±23	±10	±19	±9	
p value	<0 01		NS		NS		NS						NS		NS		

Abbreviations CL = cycle length (msec) R = retrograde Other abbreviations as in Table I

identified so that the AV node effective refractory period could not be measured

In four patients therefore the mean anterograde AV node effective refractory period increased by 7 per cent after propranolol from 328 ± 42 msec to 350 ± 29 msec but this was not statistically significant (p = 0 24) In 11 patients the mean anterograde accessory pathway effective refractory period increased by 7 per cent after propranolol from 273 ± 14 msec to 291 ± 11 msec (p = 0 01)

Atrial extrastimulation Accessory pathway conduction was absent at the time of the study in two patients in the control state and in three patients after propranolol administration so that only the AV node effective refractory period could be measured With increasing prematurity of atrial extrastimuli accessory pathway conduction failed before AV node conduction in eight patients in the control state and in seven patients after propranolol so that both the accessory pathway and AV node effective refractory periods could be measured In these patients second degree block in the normal AV pathway occurred at the level of the AV node In four patients accessory pathway conduction preserved until failure of atrial muscle or conduction In these cases the His defle could not be readily identified so that the node effective refractory period could no measured

In 10 patients therefore the mean anterog AV node effective refractory period increased per cent after propranolol from 272 ± 10 ms 280 ± 10 msec (p = 0 04) In 11 patients mean anterograde accessory pathway effe refractory period increased by 3 per cent propranolol from 281 ± 14 msec to 290 msec but this was not statistically signifi (p = 0 12) The atrial muscle effective refrac period was determined in eight patients mean atrial muscle effective refractory pe increased by 1 per cent after propranolol f 233 ± 11 msec to 236 ± 11 msec, without sta tical significance (p = 0 50)

The anterograde AV node effective refract period could be determined by both atrial pa and atrial extrastimulation in four patients the control state and after propranolol As sho in Fig 1 there was linear correlation between

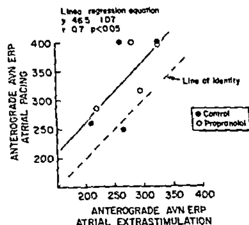


Fig 1 In the determination of the anterograde AV node effective refractory period there is linear correlation between the techniques of atrial pacing and extrastimulation The atrial pacing technique however overestimates the antero grade AV node effective refractory period, in comparison to the line of identity This is due to the parasympathetic effects of rapid atrial pacing (*AVN ERP* = atrioventricular node effective refractory period msec)

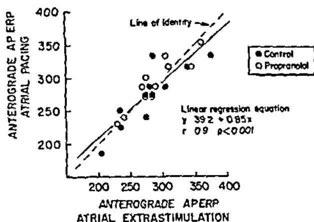


Fig 2 In the determination of the anterograde accessory pathway effective refractory period there is linear correlation between the techniques of atrial pacing and extrastimulation. The atrial pacing technique does not overestimate the ante grade accessory pathway effective refractory period in comparison to the line of identity as the parasympathetic effects of rapid atrial pacing do not affect the accessory pathway effective refractory period (*AP ERP* = accessory pathway effective refractory period msec.)

two techniques ($r = 0.7$, $p < 0.05$) but the tech nique of atrial pacing overestimated the antero grade AV node effective refractory period as determined by atrial extrastimulation by about 65 msec This may be considered to be partly because the incremental changes in cycle length during the atrial pacing technique are relatively great in comparison to the smaller incremental changes in coupling intervals during the atrial extrastimulation technique and partly because of the parasympathetic effects of rapid atrial pacing [4]

The anterograde accessory pathway effective refractory period could be determined by both atrial pacing and atrial extrastimulation in 11 patients in the control state and after proprano lol As shown in Fig 2 there was excellent linear correlation between the two techniques ($r = 0.9$ $p < 0.001$) Moreover the linear regression equa tion was very close to the line of identity This indicates that the parasympathetic effects of rapid atrial pacing do not affect the anterograde accessory pathway effective refractory period [17] It also indicates that the overestimation of the anterograde AV node effective refractory period by the atrial pacing technique is primarily due to its parasympathetic effects and not to procedural differences in the two techniques

Ventricular pacing and ventricular extrastimulation Ventricular pacing at increasing rates and the ventricular extrastimulation technique, were performed in 13 patients in the control state and in 12 patients after propranolol administration The retrograde VA effective refractory period could be determined by both ventricular pacing and in ventricular extrastimulation in 13 patients in the control state and in 11 patients after propranolol As shown in Fig 3 most points fell close to the line of identity and in these 21 cases there was excellent linear correlation between the two techniques ($r = 1.0$ $p < 0.001$) This means that in these cases the parasympathetic effects of rapid ventricular pacing did not affect the retro grade VA effective refractory period suggesting that retrograde conduction was in fact occurring across the accessory pathway Three points fell away from the line of identity and in these cases there was also excellent linear correlation between the two techniques ($r = 1.0$ $p < 0.005$) This means that in these cases the parasympa thetic effects of rapid ventricular pacing resulted in an overestimation of the retrograde VA effec tive refractory period by about 150 msec and that retrograde conduction was in fact occurring across the AV node

The retrograde accessory pathway effective refractory period could therefore be determined in the control state and after propranolol admin

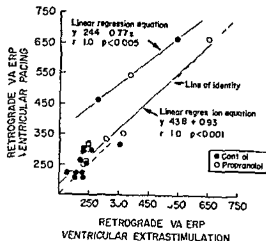


Fig 3 The parasympathetic effects of rapid *ventricular* pacing result in this technique overestimating the retrograde AV node effective refractory *period*, and therefore define the instances of retrograde AV *node* conduction as the *three points falling above the line of identity* These parasympathetic effects do not affect the retrograde *accessory* pathway effective refractory period and so the *instances of* retrograde accessory pathway conduction *are defined as the 21 points falling near the line of identity* In the determination of both the retrograde AV node and accessory pathway *effective* refractory periods there are linear correlations between the techniques of ventricular pacing and extrastimulation (*VA ERP* = ventriculoatrial effective refractory period, msec)

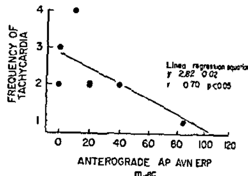


Fig 4 There is inverse linear correlation between the difference in the anterograde accessory pathway and AV node effective refractory periods and the frequency of tachycardia as determined by history A large difference is associated with *less frequent* tachycardia (*AVN* = atrioventricular node *AP* = accessory pathway *ERP* = effective refractory period msec *tachycardia frequency* daily 4+ weekly 3+ monthly 2+ yearly 1+)

istration in 10 patients by both techniques As determined by *ventricular* pacing the mean retrograde accessory pathway effective *refractory* period increased by 10 per *cent after* propranolol from 258 ± 14 *msec to* 283 ± 15 msec ($p < 0.001$) As *determined* by ventricular extrastimulation it *increased by* 4 per cent after propranolol, *from* 237 ± 15 msec to 246 ± 17 msec but this was not statistically significant ($p = 0.31$) The retrograde AV node effective refractory period could be determined *in the* control state and after propranolol administration in only one patient by both techniques As determined by ventricular pacing it increased by 18 per cent after propranolol from *462 msec to* 545 msec and as determined by ventricular extrastimulation it increased by 39 *per cent from* 280 msec to 390 msec

The mean minimum retrograde accessory pathway conduction time *in 10 patients* during ventricular pacing at the slowest *rates* with 1 1 VA conduction increased by 6 *per cent after* propranolol from 174 ± 11 *msec to* 185 ± 7 msec but this was not statistically *significant* ($p = 0.21$) The mean maximum retrograde accessory pathway conduction time during ventricular pacing at the fastest rates with 1 1 VA conduction increased by 4 per cent after propranolol from 209 ± 10 msec to 217 ± 10 msec ($p = 0.005$) The minimum retrograde AV node conduction time, in one patient increased by 8 per cent after propranolol from 255 msec to 275 msec and the maximum retrograde AV node conduction time remained 280 msec

The ventricular muscle effective refractory period was determined by ventricular extrastimulation in 11 patients in the control state and in eight patients after propranolol administration In eight patients therefore the mean ventricular muscle effective refractory period increased by 5 per cent after propranolol from 203 ± 8 msec to *213 ± 9 msec* ($p = 0.03$)

Tachycardia initiation Re entry *tachycardia* with anterograde conduction across *the AV node* and retrograde conduction across the *accessory* pathway[2,4,33,35,40] (re entry AV node-accessory pathway tachycardia) was initiated in seven patients in the control state and in eight patients after propranolol administration *In seven* patients therefore the mean cycle *length of the* tachycardia increased by 12 per cent after propranolol, *from 311 ± 14* msec *to 347 ± 19* msec ($p = 0.008$) This corresponds to a decrease in the mean rate of the tachycardia of *10 per cent* after propranolol from 193 ± 8 per minute *to* 173 ± 9 per minute The mean retrograde *accessory* pathway conduction time during the *tachycardia*

decreased by 2 per cent after propranolol from 136 ± 10 msec to 133 ± 11 msec but this was not statistically significant (p = 0 65)

Re-entry tachycardia with anterograde conduction across the accessory pathway and retrograde conduction across the AV node[2,4,33,35,0] (re entry accessory pathway-AV node tachycardia) was initiated in three patients in the control state and after propranolol administration The mean cycle length of the tachycardia increased by 5 per cent after propranolol from 275 ± 10 msec to 290 ± 6 msec but this was not statistically significant (p = 0 10) This corresponds to a decrease in the mean rate of the tachycardia of 5 per cent after propranolol from 218 ± 7 per minute to 207 ± 4 per minute The mean retrograde AV conduction time during the tachycardia increased by 5 per cent after propranolol from 210 ± 12 msec to 220 ± 10 msec but this was not statistically significant (p = 0.23)

Re entry tachycardia with anterograde and retrograde conduction across the AV node (re entry intranodal or AV node-AV node tachycardia) was initiated in one patient in the control state and after propranolol administration This patient has been previously reported [1] The cycle length of the tachycardia increased by 3 per cent after propranolol from 320 msec to 330 msec This corresponds to a decrease in the rate of the tachycardia of 3 per cent after propranolol from 188 per minute to 182 per minute The retrograde AV node conduction time during the tachycardia increased by 5 per cent after propranolol from 110 msec to 115 msec

Re entry tachycardia of either of the three types was initiated by atrial extrastimuli in eight patients in the control state and after propranolol administration The mean duration of the tachycardia zone [42] or the zone of coupling intervals of atrial extrastimuli that initiated the tachycardia decreased after propranolol from 39 ± 23 msec to 16 ± 10 msec but this was not statistically significant (p = 0 19) In many patients the duration of the tachycardia zone was 0 meaning that there was only one coupling interval of atrial extrastimuli that initiated re entry tachycardia The mean outer limit of the tachycardia zone decreased by 3 per cent after propranolol from 294 ± 19 msec to 286 ± 9 msec but this was not statistically significant (p = 0 6)

The difference between the anterograde accessory pathway and AV node effective refractory periods has been implicated as a factor in the tendency to develop re entry AV node-accessory pathway or accessory pathway-AV node tachycardia [20] Excluding the patient who developed re-entry AV node-AV node tachycardia during the study this difference could be determined in seven patients There was inverse linear correlation (r = −0 7 p < 0 05) with the historical frequency of tachycardia as shown in Fig 4 The greater the difference between the anterograde accessory pathway and AV node effective refractory periods, the smaller the likelihood of a history of frequent tachycardia According to the linear regression equation a patient with an anterograde accessory pathway-AV node effective refractory period difference of more than 140 msec would be most unlikely to have a history of tachycardia on a re entry AV node-accessory pathway or accessory pathway-AV node basis In these seven patients the mean anterograde accessory pathway-AV node effective refractory period difference in fact decreased after propranolol from 25 ± 11 msec to 21 ± 8 msec but this was not statistically significant (p = 0 27)

The tachycardia zone may be expected to be small in those patients with a large anterograde accessory pathway-AV node effective refractory period difference This relationship however could not be satisfactorily determined because of the many instances where the duration of the tachycardia zone was 0 Nevertheless, atrial extrastimuli initiated re entry AV node-accessory pathway or accessory pathway-AV node tachycardia in the control state or after propranolol in 10 of 12 cases with an anterograde accessory pathway-AV node effective refractory period difference of less than 40 msec and in none of three cases where this difference was 65 to 185 msec

During the course of the routine stimulation techniques atrial fibrillation with accessory pathway conduction[5,35,3-47] occurred in three patients in the control state and in none after propranolol administration Atrial flutter with accessory pathway conduction occurred in one of these (patient No 14) in the control state but not after propranolol The shortest RR interval of the ventricular response during atrial fibrillation was used as an estimate of the anterograde accessory pathway effective refractory period [4,47] In these three patients the anterograde accessory pathway effective refractory period as estimated by

this method was 240 180 and 160 msec (mean 193 ± 24 msec) Their anterograde accessory pathway effective refractory periods as determined by atrial extrastimulation from the high right atrial site were 235, 235 and 205 msec in the control state (mean 225 ± 10 msec) and 275, 240, and 230 msec after propranolol (mean 248 ± 14 msec) Hence if atrial fibrillation with accessory pathway conduction were to have occurred after propranolol administration in these patients the ventricular response would have been decreased by about 17 per cent 2 per cent and 12 per cent, respectively (mean 10 per cent)

Discussion

Paroxysmal tachycardia in the WPW syndrome usually occurs on a re entry basis If a suitable timed extrasystole occurs when one AV pathway is refractory and the other is not sole conduction over the latter will occur If the former pathway is now available for conduction in the reverse direction sole conduction over this will then occur[31] This allows for a re entry tachycardia circuit the components of which are the AV node, His Purkinge system ventricular muscle accessory pathway and atrial muscle The re entry tachycardia is usually conducted anterogradely across the AV node and retrogradely across the accessory pathway (re entry AV node-accessory pathway tachycardia) and occasionally in the reverse direction (re entry accessory pathway–AV node tachycardia)[2,4,33,35,40] The resultant rapid repetitive premature stimulation of the atria may initiate atrial fibrillation or flutter Atrial fibrillation and flutter in the WPW syndrome are usually conducted anterogradely across the accessory pathway[4,31,43,47] frequently resulting in a very rapid ventricular response depending on the anterograde accessory pathway effective refractory period This very rapid repetitive premature stimulation of the ventricles may initiate ventricular fibrillation[50,5]

For a drug to be effective in the WPW syndrome therefore it should (1) act directly on the atrial or ventricular muscle in such a way as to prevent the extrasystoles which initiate the other arrhythmias or to prevent or terminate atrial and ventricular fibrillation (2) depress part or all of the re-entry circuit so as to prevent terminate or slow the rate of the re entry tachycardias thereby also preventing atrial and ventricular fibrillation, or to slow the ventricular response in atrial fibrillation and flutter in the case of depression of anterograde accessory pathway conduction thereby also preventing ventricular fibrillation

An electrophysiologic assessment of a drug in the WPW syndrome therefore requires assessment of its effects on the atrial and ventricular muscle, and on the anterograde and retrograde conduction characteristics of the other components of the re entry circuit

Effective refractory periods The intravenous administration of propranolol 0 1 mg/Kg failed to increase the atrial muscle effective refractory period, and the ventricular muscle effective refractory period was increased by only 5 per cent The anterograde AV node effective refractory period as determined by atrial pacing was not increased and as determined by atrial extrastimulation was increased by only 3 per cent The anterograde accessory pathway effective refractory period as determined by atrial pacing was increased by only 7 per cent and as determined by atrial extrastimulation was not increased.

As compared to atrial extrastimulation the technique of atrial pacing overestimates the anterograde AV node effective refractory period but not the anterograde accessory pathway effective period (Figs 1 and 2) This disparity between the two techniques in the case of the anterograde AV node effective refractory period has been previously noted in non WPW patients[33] There is no such disparity in the case of dogs who have undergone vagotomy[34] so that this effect appears to be due to the parasympathetic influences of rapid atrial pacing[34] which increase the AV node effective refractory period but not the accessory pathway effective refractory period[17] This phenomenon was used to determine in which cases the techniques of ventricular pacing and extrastimulation estimated the retrograde accessory pathway effective refractory period where there was no disparity between the two techniques and in which cases the retrograde AV node effective refractory period was estimated where the technique of ventricular pacing overestimated the VA effective refractory period as compared to that of ventricular extrastimulation (Fig 3)

In this way it was found that the retrograde accessory pathway effective refractory period as determined by ventricular pacing was increased by 10 per cent after propranolol administration.

and as determined by ventricular extrastimulation was not increased. The retrograde AV node effective refractory period in the control state and after propranolol could be determined in only one patient and was increased by 18 per cent and 39 per cent as determined by ventricular pacing and extrastimulation respectively. Conclusions in regard to the effect of propranolol on the retrograde AV node effective refractory period cannot be made on the basis of a single study but even a significant effect on this site would influence only the unusual form of re-entry tachycardia in the WPW syndrome, the re-entry accessory pathway-AV node tachycardia.

Otherwise, as propranolol did not significantly increase the effective refractory period of any part of the re-entry tachycardia circuit studied in either anterograde or retrograde directions, it will not by this mechanism prevent or terminate the re-entry tachycardias or slow the ventricular response in atrial fibrillation and flutter. If the ventricular rate in atrial fibrillation is an important factor in initiating ventricular fibrillation, neither is propranolol likely to prevent the initiation of ventricular fibrillation by this mechanism.

Tachycardia initiation. The initiation of re-entry tachycardia by atrial extrasystoles may be expected to be less likely when the range of coupling intervals of atrial extrastimuli that initiate re-entry tachycardia is found to be small. Propranolol did not significantly decrease the duration of this "tachycardia zone." If the outer limit of the tachycardia zone is decreased or shifted to the left, an atrial extrasystole with a coupling interval at this outer limit will no longer initiate re-entry tachycardia. Propranolol failed to significantly decrease the outer limit of the tachycardia zone.

The greater the difference between the anterograde effective refractory periods of the accessory pathway and the AV node, the greater the likelihood of conduction of atrial extrasystoles solely across the AV node, which is the initial requirement for re-entry AV node–accessory pathway tachycardia. The re-entry circuit, however, also includes retrograde accessory pathway conduction and re-entry will not occur if the retrograde accessory pathway effective refractory period is too long. A long anterograde accessory pathway effective refractory period, making tachycardia more likely to be initiated by atrial extrasystoles, may be associated with a long retrograde accessory pathway effective refractory period, making tachycardia less likely to occur. It is likely, therefore, that there is an optimal anterograde accessory pathway–AV node effective refractory period difference for initiation of re-entry tachycardia by atrial extrasystoles, such that if this difference is smaller, tachycardia is less likely to occur because the anterograde "electrical window" is smaller, and if this difference is greater, tachycardia is less likely to occur because the associated retrograde accessory pathway effective refractory period is too long. In this case Fig. 4 should resemble a parabola rather than a straight line. Similar considerations would apply in regard to the retrograde AV node–accessory pathway effective period difference and the initiation of re-entry tachycardia by ventricular extrasystoles. Over all, however, it appears that symptomatic tachycardia is less likely when there is a large difference between the anterograde effective refractory periods of the accessory pathway and the AV node. Propranolol failed to significantly alter this mean difference and so did not affect the propensity of extrasystoles for initiating re-entry tachycardia.

Not surprisingly, therefore, re-entry AV node–accessory pathway tachycardia was initiated during the course of the stimulation studies in seven patients in the control state and eight after propranolol. Re-entry accessory pathway–AV node tachycardia was initiated in three patients before and after propranolol.

Tachycardia rate. The rate of the re-entry tachycardias will depend on the total conduction time through the re-entry circuit either anterogradely or retrogradely. Propranolol did not significantly increase the anterograde AV node or accessory pathway conduction time during sinus rhythm. We could not determine the anterograde AV node conduction time during rapid atrial pacing, as the His deflection could not then be readily identified. Propranolol has been reported to increase the anterograde AV node conduction time but not the anterograde accessory pathway conduction time during rapid atrial pacing.[15, 55-57]

Propranolol did not increase the retrograde accessory pathway conduction time during basic ventricular pacing and increased that during rapid ventricular pacing by only 4 per cent. The retrograde AV node conduction time in the

control state and after propranolol could be determined in only one patient in whom propranolol increased the minimum retrograde AV node conduction time by 8 per cent and did not increase the maximum retrograde AV node conduction time

In the re entry AV node–accessory pathway tachycardias initiated during the stimulation studies propranolol caused a decrease in rate of only 10 per cent This was due to an increase in the anterograde AV node conduction time at rapid rates of conduction as the retrograde accessory pathway conduction time was not increased In the re entry accessory pathway–AV node tachycardias initiated propranolol did not decrease the rate or increase the retrograde AV node conduction time If the rate of the re entry tachycardias is an important factor in initiating atrial fibrillation or flutter, propranolol is not likely to prevent these arrhythmias by this mechanism

No specific attempt was made to initiate atrial fibrillation or flutter by atrial pacing at very rapid rates During the course of the routine stimulation studies, however, atrial fibrillation occurred in three patients in the control state one of whom also developed atrial flutter Neither arrhythmia occurred after propranolol administration Although a finding of some interest numbers are too small for this to be statistically significant The ventricular response in atrial fibrillation correlates with the anterograde accessory pathway effective refractory period [4, 47, 49] so that in this way it was determined that if atrial fibrillation were to have occurred after propranolol in these three patients the ventricular response would have been decreased by only 10 per cent

Rosen and associates[18] *reported some effects of* a fixed dose of propranolol 5 mg intravenously in nine patients with the WPW syndrome The atrial extrastimulation technique was performed in only two patients however and as assessed by the atrial pacing technique the anterograde AV effective refractory periods were not always determined by increasing the rate of atrial pacing to the point of failure of 1 1 AV conduction Studies of retrograde VA conduction atrial or ventricular muscle conduction and tachycardia initiation were not performed Propranolol did not increase the anterograde accessory pathway effective refractory period and on review of their data the increase in the anterograde AV node effective refractory period of about 11 per cent was not statistically significant The same group later reported preliminary data[26] showing no increase in the retrograde VA effective refractory period as determined by ventricular pacing alone and no decrease in the duration or outer limit of the 'echo zone' Re entry tachycardia was initiated in 10 of 13 patients in the control state and in seven after propranolol with a decrease in rate of only 7 per cent, due to an increase in the anterograde AV node conduction time

The failure of propranolol in our patients to decrease the heart rate to a greater extent or to increase the anterograde AV node effective refractory period may be unexpected In the supine position however, there is variable response of the heart rate in normal individuals after propranolol,[58] according to the dependence of the heart rate on sympathetic activity[5] In non WPW patients using the same dose of propranolol as in our study Seides and colleagues[55] found an increase in the anterograde AV node effective refractory period as determined by atrial pacing of 16 per cent but as determined by atrial extrastimulation an increase of only 7 per cent Wu and co workers studied a group of non WPW patients with re-entry intranodal tachycardia On review of their data the anterograde AV node effective refractory period as determined by atrial extrastimulation, in five patients combined with that of the slow pathway in seven patients was not significantly increased after propranolol

Clinical correlation As intravenous propranolol 0 1 mg/Kg has slight or no effect on the electrophysiologic parameters of the WPW syndrome it is unlikely to be effective as acute therapy *in this syndrome*

A number of features of relevance in the WPW syndrome however, were not able to be assessed by the electrophysiologic studies performed. These include any possible direct action of propranolol on the atrial or ventricular muscle in such a way as to prevent the extrasystoles which initiate the re entry tachycardias or to prevent or terminate atrial fibrillation and flutter or ventricular fibrillation The studies moreover were performed after the intravenous administration of propranolol and chronic oral use of a drug may not parallel acute intravenous use

It is felt however that propranolol is also

unlikely to be effective as a primary agent in the prophylaxis of the WPW syndrome unless propranolol administered on a chronic oral basis has significant additional electrophysiologic effects.

Summary

Fourteen patients with the Wolff Parkinson White (WPW) syndrome were studied by means of intracardiac stimulation techniques before and after the intravenous administration of propranolol 0 1 mg /Kg There was no significant change or only a slight increase in the effective refractory periods of all parts of the re entry tachycardia circuit studied in either anterograde or retrograde directions Re entry tachycardia was initiated in nine patients in the control state and in 10 patients after propranolol The rate of re entry atrioventricular node-accessory pathway tachycardia was decreased but by only 10 per cent The duration and outer limit of the tachycardia zone of atrial extrastimuli were not significantly decreased Propranolol by rapid intravenous infusion administration is unlikely to be effective primary therapy for PSVT in the WPW syndrome

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Case reports

Unusual echocardiographic findings in pericardial tamponade

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M mode echocardiographic scanning has been known to be a sensitive and reliable technique for the detection of pericardial effusion[1,2] The diagnosis is established by the demonstration of an echo free space between the left ventricle and the posterior pericardium This space is said to disappear near the left atrioventricular junction on a continuous scan from the apex of the left ventricle to the aortic root It is generally felt that fluid cannot accumulate behind the left atrium because of the nature of the reflection of the pericardium around the great vessels on the posterior surface of the heart This report describes a case of pericardial tamponade in which M mode echocardiography revealed definite fluid behind the left atrium Other unusual echocardiographic features of this case were apparent prolapse of the mitral valve and markedly exaggerated motion of the heart as a whole A normal EF slope was recorded despite the presence of pericardial tamponade

Method

M mode echocardiographic examinations were performed before and during pericardial tamponade and after removal of pericardial fluid All the studies were performed using an Irex echograph and a transducer with a focal length of 7 5 cm a diameter of 0 5 inch and frequency of 2 25 MHz

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Case report

A 38-year-old white male with chronic renal failure being maintained on intermittent hemodialysis was admitted with retrosternal chest pain Physical examination revealed a heart rate of 100 per minute and blood pressure of 100/80 mm Hg Cervical veins were not distended Ausculation over the precordium revealed an S gallop and a loud pericardial rub The lungs were clear An electrocardiogram revealed sinus tachycardia and repolarization changes suggestive of pericarditis Chest x ray at the time of admission showed moderate cardiomegaly clear lung fields, and no pleural effusions. An echocardiogram done one month prior to the present admission had shown no gross abnormalities except left ventricular hypertrophy The study done at the time of admission showed a posterior pericardial effusion demonstrable both behind the left ventricle and left atrium (Fig 1) Three days after admission the patient suddenly became dyspneic tachycardic and hypotensive The central venous pressure was elevated to 17 cm of water An echocardiogram at this time showed a definite increase in the posterior pericardial effusion In addition two new abnormalities were also recorded. These included (1) wide swinging movements of the entire heart and (2) intermittent mitral valve prolapse (Fig 2) The diastolic closure of mitral valve (EF slope) which previously had been normal was unchanged The patient then underwent an open pericardiotomy during which 680 c c of fluid were removed with rapid improvement in his clinical staus An echocardiogram done 3 days afterward showed complete disappearance of the previously noted abnormalities

Discussion

Effusion behind the left atrium Pericardial fluid is demonstrable echocardiographically as an echo free space behind the left ventricle As the transducer is angulated cephalad to the point where the left atrium becomes visible behind the posterior aortic wall this echo free space is no longer visualized Recently however Lemire and associates[4] and Green and colleagues reported on pericardial effusion posterior to the left atrium The latter group suggested the following explanation for effusion behind the atrium The visceral

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Fig 1 M mode echocardiographic scan showing pericardial effusion—both behind the left atrium and left ventricle *(arrows)*

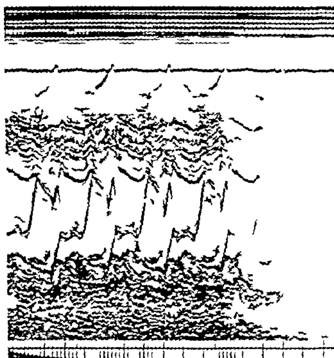


Fig 2 *Arrow* shows mitral valve prolapse

pericardium on the posterior surface of the heart is reflected onto itself to form the parietal pericardium The arrangement of the great vessels on the posterior aspect of the heart is such that the pericardium is pulled taut but not attached between the points of its reflection onto these two vessels this reflection divides off a part of the pericardial sac referred to as the oblique sinus which is closed superiorly and to the right but is open inferiorly and to the left While in most pericardial effusion this part is blocked by the tautness of the pericardium behind the atrium this anatomic barrier may not be effective preventing such an accumulation of fluid es cially if the fluid is under pressure The fact th our patient developed pericardial tampona soon after the demonstration of fluid behind t atrium may suggest that the fluid was inde under great pressure If this is so one might ev be able to predict pericardial tamponade based this finding

Mechanism of pseudo mitral valve prolap and swinging heart Since the advent of ech cardiography the syndrome of mitral va prolapse has been increasingly diagnosed and i important to avoid misinterpretation Mit valve motion as observed echocardiographically the result of intrinsic mitral leaflet moveme and to a lesser extent mitral ring and total he motion[6,7] Entire cardiac motion is exaggerated the presence of a large pericardial effusion th results in the appearance of an exaggerated pos rior movement of mitral valve with leaf prolapse Observation of the motion of the en heart will help to distinguish this pseudo prolap from true prolapse Systolic anterior moveme of the mitral valve has also recently be observed in pericardial effusion although t mechanism is not quite clear According to Na and co workers the presence of significant fl collections behind the left atrial cavity associat with dynamic movements and systolic pe formation of the left atrial wall compound t total swinging motion of the heart in the perica dial sac producing motion artefacts of card valves It is interesting that all their patie showing abnormalities of motion of cardiac val had effusion behind the left atrium

Mitral EF slope The diastolic closure slope of the mitral valve (EF slope) is related to the rate of left ventricular filling and a decreased EF slope is seen in those conditions where there is an increased resistance to left ventricular filling such as cardiac constriction[6] It has been stated that a normal EF slope is evidence against the presence of pericardial tamponade However in the present patient the EF slope was found to be normal before during and after correction of pericardial tamponade It is possible that in pericardial tamponade the diminished posterior movement of the anterior mitral leaflet during closure could appear to be increased by the anterior movement of the entire heart during diastole No decrease in EF slope in pericardial tamponade was observed by Zoneraich and colleagues in their recent study Thus the undue reliance on a decreased EF slope may limit the sensitivity of the echocardiogram in the diagnosis of pericardial tamponade

Conclusion

As in the present case serial echocardiographic studies may be necessary for the correct interpretation of some unusual features seen in pericardial tamponade An important finding in patients with pericardial effusion may be fluid behind the left atrium since it appears to presage cardiac tamponade although a normal EF slope may be preserved in such patients despite cardiac constriction

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Left atrial myxoma False negative echocardiographic findings in a tumor demonstrated by coronary arteriography

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Atrial myxoma is an intracavitary tumor of the heart whose diagnosis prior to 1951 was seldom made before postmortem examination or thoracotomy [1] The clinical diagnosis of left atrial myxoma was first made by angiocardiography in 1951 [2] and since then there have been a number of reviews in which the clinical pathologic angiocardiographic, and echocardiographic features have been well documented [1, 3-12]

This report illustrates two unusual features tumor vascularity and difficulty in echocardiographic demonstration of a myxoma Demonstration of atrial myxoma by coronary arteriography has been reported in only five previous cases and in each instance the appearance was one of tumor vascularity or coronary neovascularity

Case presentation

A 67 year old housewife was admitted to the Montreal General Hospital on March 27 1977 with a two week history of progressive shortness of breath lower extremity swelling and syncope She had first come to medical attention in July 1976 with complaints of general fatigue dyspnea and retrosternal chest tightness on exertion She denied any past history of rheumatic fever or prior knowledge of a heart murmur There was no family history of heart disease and the remainder of the cardiopulmonary enquiry was noncontributory The findings on physical examination were characteristic of mitral stenosis A clinical diagnosis of mitral stenosis [illegible] concomitant coronary artery disease was made An echo[illegible] diogram (Fig 1) apparently confirmed the diagnosis of mi[illegible] stenosis Institution of appropriate therapy resulted in moderate clinical improvement and she remained stable [illegible] functional Class II level over the following eight mo[illegible] Two weeks prior to hospital admission her dyspnea worse[illegible] with the development of orthopnea paroxysmal noctur[illegible] dyspnea and marked lower extremity edema She experie[illegible] two episodes of syncope both occurring on arising from [illegible] supine position

On admission to hospital physical examination revealed [illegible] moderately obese female with a blood pressure of 140 [illegible] Hg and an irregular pulse of 95/minute Jugular ve[illegible] pressure was 3 cm above the sternal angle with a prominen[illegible] wave Carotid pulsations were normal. The apex beat [illegible] normal in position and character There was an eas[illegible] ble left parasternal heave The first heart sound was [illegible] tuated The second heart sound had a markedly accentua[illegible] pulmonary component There was an early diastolic [illegible] interpreted as an opening snap followed by a III/VI [illegible] diastolic rumble heard maximally at the lower left s[illegible] border and apex There was a short II/VI systolic [illegible] murmur at the lower left sternal border with poor radia[illegible] There was marked pitting edema to the level of the [illegible] bilaterally The remainder of the physical examination [illegible] normal

An electrocardiogram showed sinus rhythm at a ra[illegible] 98/minute with frequent ventricular extrasystoles. The fro[illegible] tal plane electrical axis was 105 degrees and there were P [illegible] abnormalities consistent with left atrial enlargement. T[illegible] chest roentgenogram showed left atrial enlargement [illegible] redistribution of pulmonary venous flow and a small [illegible] pleural effusion There was no evidence of calcification [illegible] the cardiopericardial silhouette The hemoglobin was [illegible] gms and the erythrocyte sedimentation rate was elevated [illegible] 34 mm/hour There were no other laboratory abnormali[illegible] ties.

The patient's clinical condition stabilized over the follow[illegible] days in hospital although symptoms and signs of conge[illegible] heart failure were slow to resolve

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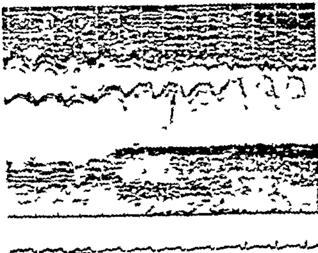


Fig 1 Initial M mode echocardiogram showing a sweep from the aortic root to the mitral valve There is duplication of the echo complex from the anterior leaflet of the mitral valve (*arrow*) but no frank tumor echoes. The left atrium behind the aortic root is clear



Fig 2 Left ventricular angiogram 30 degrees right anterior oblique view The leading edge of the tumor (*arrows*) can be seen as it prolapses across the mitral valve during diastole

Cardiac catheterization was performed on April 6 1977 Using the percutaneous transfemoral approach right and left heart catheterizations were completed There was moderate elevation of the right ventricular and pulmonary artery pressures measuring 62/11 and 62/28 mm Hg respectively The mean pulmonary wedge pressure was elevated at 30 mm Hg and there was a 14 mm. Hg gradient across the mitral valve at end diastole Cardiac index aortic and left ventricular pressures were normal

A left ventricular angiogram revealed a normal sized left ventricle with mild regurgitation of contrast material across the mitral valve A large filling defect estimated to be 4 to 5 cm in diameter was observed to prolapse across the mitral valve from the left atrium during diastole (Fig 2)

Coronary arteriography was performed using a single multi purpose catheter according to the method of Schoonmaker and King The right coronary system was unobstructed At the crux of the heart the right coronary artery ga e off posterior descending branches and a large extraneous vessel which was seen to supply the left atrial filling defect with a resultant tumor blush (Fig 3) In addition to the larger single vessel numerous smaller vessels originating from the right coronary system also supplied the tumor mass The left coronary system was also unobstructed A smaller branch arising from the proximal portion of the circumflex artery was seen to supply the left atrial mass (Fig 4)

After the angiographic demonstration of the tumor echo cardiographic examination was repeated using both 3 5 and 2 25 MHz transducers and a variety of gain and sensitivity settings A contact B scan using an image scan converter was performed and by adjustments of the gray scale the tumor echoes could be faintly visualized (Fig 5)

At surgery the left atrial tumor was found to be attached by a broad stalk to the interatrial septum and measured approximately 3 × 5 cm The tumor was excised without difficulty The operative course was complicated by the development of high degree atrioventricular block requiring temporary ventricular pacing.

Subsequent gross and microscopic pathology confirmed the myxomatous nature of the lesion On gross examination the external surface was coarsely lobulated and the cut surface was gelatinous. Histologic sections of samples from the center and the base of the lesion showed numerous blood vessels of varying size some defined only by endothelial like cells and others with a well developed fibromuscular wall (Fig 6) Most of the lesion was composed of stellate and polygonal tumor cells immersed in an alcianophilic myxomatous stroma (Fig 7)

Discussion

Despite the well documented clinical manifestations and abnormalities seen in association with left atrial myxoma the diagnosis remains difficult to make on clinical grounds alone The present case reemphasizes the need for a high degree of clinical suspicion and the use of ancillary investigative tools to either confirm or negate the presence of such a lesion

The case described illustrates two rather uncommon features first the demonstration of the tumor by selective coronary arteriography and second the difficulty encountered in establishing the correct diagnosis by echocardiography

The incidence of tumor vascularity in atrial myxoma of sufficient degree to be visualized by coronary arteriography is unknown Tumor vascularity in left atrial myxoma was first described by Marshall and associates in 1969[1] Since then four additional cases have been



Fig 3 Right coronary artery injection 30 degrees left anterior oblique view The tumor shows a marked vascular blush. A large extraneous vessel can be seen arising from the right coronary artery at the crux of the heart to supply the tumor (*arrow*)



Fig 4 Left coronary artery injection 50 degrees left a... oblique view The vascular blush is less marked but clearly visible (*enclosing arrows*) A large atrial branch o... left circumflex can be seen supplying the tumor (*arrow*)

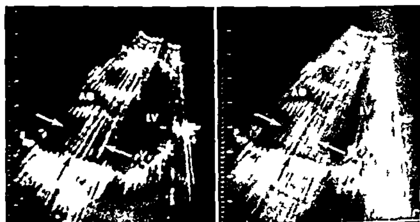


Fig 5 Contact B scan at two different contrast settings In this long axis view the tumor (*arrows*) can be faintly visualized in the left atrium behind the aortic root *AO* aortic root *LV* left ventricular cavity

described including the demonstration of blood supply to a right atrial myxoma [15,18] In none of the previously described cases was the diagnosis suspected prior to the catheterization study and the patients most commonly underwent the study as part of the investigation for mitral valve disease coronary artery disease or an undiagnosed murmur The right coronary artery was the vessel involved as a source of blood supply in all previously described cases except for the case reported by Chan which exhibited blood supply from both right and left coronary arterial systems Neovascularity is not specific for tumors as was pointed out by Standen in 1975

when he described a case of left atrial throm... demonstrated by selective coronary arteri... raphy More recently Soulen and colleag... have described 15 cases of coronary neovascul... ty nine of which were associated with left at... thrombus in the presence of mitral stenosis Th... further point out that the coronary arteriogra... ic findings in patients with neovascularized l... atrial thrombus do not necessarily disting... thrombus from myxoma In addition to thromb... and myxoma Marshall and associates state t... other diagnoses including collateral circulatio... coronary artery disease and those variants oc... sionally associated with pulmonary atresia a...



Fig 6 Low power photomicrograph of a vascular area of the myxoma Irregular vascular channels are prominent and several contain blood. (Original magnification ×120)



Fig 7 Higher magnification photomicrograph than *Fig 6* On the left the myxoma cells are arranged in delicate anastomosing cords. On the right myxoma cells are isolated or grouped in small clusters. (Original magnification ×300)

Tetralogy of Fallot should be considered when such neovascularity is observed

Prior to the use of echocardiography the principal method of diagnosing left atrial tumors was by angiography The latter procedure carries some risk and echocardiography has largely supplanted angiography as the primary diagnostic tool The technical pitfalls false positive and false negative results occasionally encountered in the echocardiographic examination for left atrial myxoma have been pointed out by Feigenbaum[12]

Despite careful attention to the sources of error and even though the patient was examined retrospectively after the diagnosis was known demonstration of the tumor was exceedingly difficult in the case presented In the case described by Marshall and colleagues[3] echocardiographic demonstration was claimed It is unknown whether echocardiography was utilized in the other cases of left atrial myxoma which exhibited an angiographically demonstrable vascular supply The single case of right atrial myxoma described by Berman and co workers[4] was not demonstrable by echocardiography even though this method of examination was utilized in a retrospective fashion

The difficulty in the echocardiographic demon

stration of the lesion described in the present case may have been due to the highly vascular nature of the lesion with a resultant loss of the necessary acoustic reflectivity There is obviously relatively little acoustic mismatch between the blood in the vascular tumor and the blood in the left atrium In the successful echocardiographic demonstration described by Marshall and colleagues[15] the magnitude of neovascularity appeared to be much less than in our case Extensive neovascularity may represent a new form of false negative with respect to echocardiographic examination for left atrial myxoma, although examination of similar cases will be needed for confirmation

Summary

A report of left atrial myxoma discovered at coronary arteriography by virtue of unusual tumor vascularity is presented in which establishing the diagnosis by means of echocardiography proved difficult The difficulty may have been due to the highly vascular nature of the tumor with resultant loss of the acoustic reflectivity required for echocardiographic demonstration Previous cases in which left atrial myxomas have shown arteriographically demonstrable tumor vascularity are reviewed

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Clinical pathologic conference

Sudden death in a narcotic addict four months following aortic valve replacement

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DR STEPHEN FACTOR The case to be discussed today concerns a 47 year old Puerto Rican male with a history of aortic valve replacement who was brought to the emergency room complaining of severe chest pain

The patient was a known heroin addict since age 14 who was on methadone maintenance for the last 6 years He was in his usual state of health until 6 months prior to admission when he developed peripheral edema and dyspnea on exertion He was admitted to a local hospital where his blood pressure was noted to be 140/50 mm Hg and he was found to have diffuse petechiae cardiomegaly hepatosplenomegaly a murmur of aortic regurgitation and mild disorientation VDRL was positive Multiple blood cultures were positive for enterococcus and candida organisms He was treated with antibiotics and amphotericin B and he was transferred to the Hospital of the Albert Einstein College of Medicine

On admission the diagnosis of candidal and enterococcal endocarditis was confirmed and he was treated with penicillin streptomycin and amphotericin B Neurological symptoms developed including a right sided motor weakness which were attributed to a possible cerebral embolus or a brain abscess He did not respond well to medical treatment and one week after admission he underwent aortic valve replacement with a prosthetic Capetown valve

At surgery the patient was noted to have a grossly enlarged left ventricle moderate dilatation of the ascending aorta and a completely insufficient aortic valve Pathological examination of the resected valve revealed partial calcification and candida endocarditis He tolerated the surgical procedure well, but postoperatively he developed transient renal and pulmonary insufficiency Following a prolonged hospitalization however at the time of discharge 2½ months after surgery he was afebrile blood cultures were negative and the blood urea nitrogen was normal

He was well for 6 weeks when he suddenly developed severe crushing substernal chest pain became cyanotic and collapsed He was brought to the emergency room and was found to have a blood pressure of 60 mm Hg by palpation *Auscultation of the chest revealed bilateral rales* Prosthetic aortic valve sound and an S were heard The central venous pressure was 20 cm H_2O The electrocardiogram showed massive ST elevations across the precordium Laboratory data were generally unremarkable The patient had a cardiac arrest shortly after admission and resuscitation attempts were unsuccessful

Dr Frishman will now discuss the clinical protocol

DR WILLIAM FRISHMAN The case presented here today is that of a 47 year old Hispanic male with a long history of narcotic abuse who developed endocarditis on his native aortic valve Both enterococci and Candida tropicalis were grown from the blood His medical course was a stormy one with complications of congestive heart fail

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ure cerebral dysfunction, and renal involvement, and he was treated with intravenous penicillin amphotericin B and IM Streptomycin However, because of his failure to respond to this regimen he underwent surgical removal of his native aortic valve with replacement by a Capetown prosthetic valve His postoperative course in the hospital was complicated by persistent azotemia, however, he completed his antibiotic regimen with resolution of his cardiovascular neurologic, and renal difficulties He was discharged from the hospital only to return four months later without any specific problem noted in the interim His final admission was prompted by the sudden onset of chest pain and despite urgent medical attention he developed cardiopulmonary arrest and could not be resuscitated

I will begin my discussion with the problem of endocarditis in the drug abuser since it may shed some light on what transpired during the patient s final admission This case is remarkable because most cases of endocarditis seen in drug abusers occur in their late twenties and the finding of a 47 year old addict with this condition is quite unusual[1] Though the patient was in a methadone maintenance program this fact does not rule out continued intravenous drug abuse The widespread increase in the use of narcotics by the intravenous route has been responsible for important changes in the incidence and clinical spectrum of infective endocarditis[2] Valvular infection is responsible for 10 per cent of the deaths in heroin addicts[2] The endocarditis usually affects normal native valves[2, 3] and even with the best medical regimens carries a mortality rate of up to 75 per cent[2] This high mortality rate probably relates to the advanced stage in which addicts usually present and the virulence of the microbes involved The staphylococcus organism is seen in over 50 per cent of patients[2] Candida species and gram negative bacilli are responsible for about one third of endocarditis cases in contrast to less than 5 per cent in non addicts Streptococcus viridans the most common cause of endocarditis in non addicts is unusual in many of the reported cases of endocarditis in drug addicts

The endocarditis of drug abusers as in this case usually affect the left sided valves though 20 per cent of patients will present with predominant right sided involvement For some reason heroin addicts in Washington D C have more frequent right sided endocarditis than left sided involvement[4] As demonstrated by this patient the medical therapy for endocarditis in heroin abusers is for the most part unsatisfactory[3] We are fast learning that the judicious use of surgery is the only effective means for bacterial cure[3] Endocarditis can be equated with an abscess of the valve where incision and drainage will provide the only curative therapy

The patient had involvement of his aortic valve with aortic insufficiency related to a combined infection of enterococci and Candida Enterococci are relatively uncommon organisms in heroin endocarditis[2, 4] Despite the fact that the patient had a positive VDRL which was most likely secondary to the endocarditis the chance of syphilitic aortitis as the cause for the aortic insufficiency is extremely improbable It is of interest that the patient grew out *Candida tropicalis* from the blood for in a large series of fungal endocarditis reported from New York University *Candida tropicalis* was always seen in drug abusers rather than *Candida albicans*[5]

Candida endocarditis is a lethal condition and for the most part removal of the valve is the only possible means for cure[5, 6] The large valvular vegetations are usually resistant to antibiotic penetrance and these vegetations characteristically embolize to large peripheral arterial vessels[2] In this patient the cerebral dysfunction and the parietal lesion noted on brain scan may very well have been a consequence of cerebral emboli Neurologic complications are often seen in endocarditis with patients presenting with either localizing neurologic signs a toxic encephalopathy, meningitis or even cerebral hemorrhage from rupture of mycotic aneurysms

The patient had severe aortic insufficiency which could be detected by the wide aortic pulse pressure and a very important sign the absence of or a diminished first heart sound The first heart sound is decreased in its intensity when there is a high left ventricular diastolic pressure which causes the premature closure of the mitral valve By the time mechanical systole begins the mitral valve is already in a closed position, so the first heart sound is not well auscultated if at all An echocardiogram would have been extremely useful to demonstrate premature closure of the

valve fluttering of the aortic valve or the state of left ventricular function

The decision to operate on this patient was probably prompted by his failure to respond to the antibiotic regimen He underwent removal of his aortic valve and replacement with a Lancer Capetown caged disc valve There is little mention of what was found at surgery but one would guess from the clinical data presented that the native aortic valve was completely useless There is no mention whether there was any intraoperative inspection of the mitral valve or the coronary arteries There is also no mention of whether the patient underwent a cardiac catheterization I am glad there is no mention of this because angiography and catheterization in the face of endocarditis carries with it the risk of dislodging a vegetation from the valve

The patient s postoperative course was complicated by persistent azotemia which was felt to be secondary to his antibiotic regimen since amphotericin B and streptomycin are notorious nephrotoxin Of course the renal dysfunction may have been related to the endocarditic process The patient was able to complete his course of amphotericin B with ampicillin substituted for penicillin and streptomycin He was discharged after spending 2½ months in the hospital with some resolution of his neurologic cardiac and renal problems In the four month period following his discharge from the hospital there is little mention of what transpired Was the patient instructed about the importance of antibiotic prophylaxis for dental procedures? Was the patient on an adequate anticoagulation regimen which is quite important with plastic prosthetic valves?[7, 8] When the patient was examined in follow up were there good prosthetic heart sounds or the development of new murmurs? Were follow up x rays revealing?

There are three conceivable causes for the patient s terminal illness a process unrelated to the heart disease and cardiac surgery underlying heart disease independent of the valve problem per se and finally a consequence of the prosthetic valve insertion I shall ignore the possibility that the final event was not related to either the heart disease or the prosthetic valve because the manner of death appeared to be a circulatory one

Despite the continuing advances in surgical techniques and postoperative care, and the improvements in prosthetic valve design complications following valve replacement remain a substantial source of morbidity and mortality[7, 8] These morbid complications can be divided into early within two months postoperative or late after two months

The early complications include prosthetic valve dysfunction ventricular failure or low cardiac output syndrome bleeding technical mishap central nervous system catastrophe associated undiagnosed or uncorrected valve disease and infection at the site of prosthesis attachment The bulk of this early mortality occurs within two weeks following surgery[7] The fact that the patient survived four months following surgery would suggest that a mechanically deficient valve was not inserted Additionally he seemed to have recovered from his low output syndrome, his renal insufficiency and his neurologic problems

The late causes of death following prosthetic valve implantation include prosthetic valve dysfunction prosthetic thrombosis and infective endocarditis[7] In contrast to the early complications an extremely high frequency of thromboembolic events with associated cerebral bowel and myocardial infarctions are seen Twenty per cent of patients have a sudden death for no apparent cause but probably related to an arrhythmia[7] A percentage of patients have underlying cardiac disease and left ventricular dysfunction The left ventricular dysfunction may be a consequence of the preoperative myocardial state or as a result of the operation itself Hepatitis and complications of anticoagulant therapy are also described in late mortality figures

Having gone through this ghoulish list I hasten to add that the results actually are good in the majority of patients in whom mitral or aortic prosthetic valves or both are inserted and the complications that I have mentioned have been found in a very small proportion of the cases in large series With the recent increased use of tissue valves the frequency of thromboembolism and endocarditis has been considerably reduced[2]

With these considerations in the background I shall turn to the electrocardiogram in a search for clues to what happened in this case The first

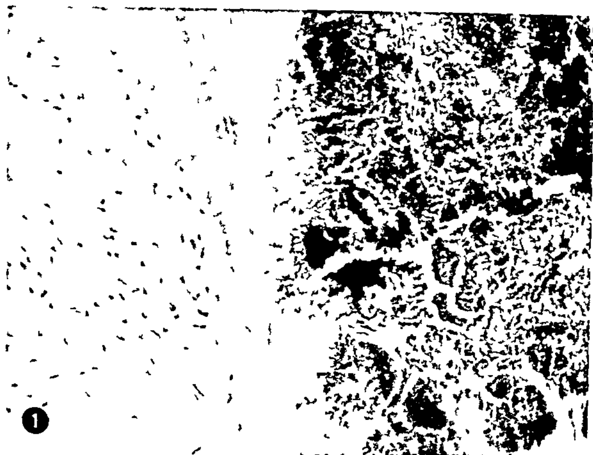


Fig 1 A portion of the aortic valve removed surgically during the first hospital admission *The valve tissue on the left* shows fibroblastic proliferation and minimal inflammation *The large vegetation on the right* is composed of numerous budding yeast and pseudohyphae *(stained dark in this picture)* consistent with Candida organisms No tissue invasion is present in this field (PAS stain original magnification ×189)

hospital admission tracing showed a regular sinus rhythm with a rate of 75 and an axis of 60 degrees There were T wave inversions in Leads V_1 and V and essentially non specific ST segment abnormalities The electrocardiogram during the patient s last admission demonstrated generalized ST and T wave elevations across the precardium and he promptly had a cardiopulmonary arrest from which he could not be resuscitated Taking the electrocardiogram and the patient s sudden demise into consideration I believe that the patient had a myocardial infarction and a terminal arrhythmia If so what caused it? First of all coronary occlusion must be considered He was 47 years old which was certainly old enough but his coronary arteries were not described to be grossly abnormal during surgery I think a more likely consideration is the possibility of a coronary embolus Bacterial endocarditis of the prosthetic valve or a bland thrombus originating on the aortic valve prosthesis and breaking off to occl one or more coronary arteries can cause myocardial infarction

In discussing bland thrombi as the cause of a embolus it is important to remember that thromboembolic complications have been a contin and distressing problem with prosthetic he valves The term thromboembolism has generally been used to include both fibrin deposition or neointimal formation on the prosthesis and subsequent systemic embolization of the material [7,8] Detection of thrombus on a prosthesis depends primarily on the presence and demonstration of some degree of prosthetic valve dysfunction due to impaired poppet motion or decreased area of the valve orifice Diagnosis can be accomplished with reasonable accuracy by careful cardiac auscultation and the use of phonocardiographic techniques Frequently the patient presents after a clinically obvious sys em



Fig 2 The surgically excised valve and a portion of the Candida vegetation have been photographed in polarized light Numerous birefringent particles are apparent within the valve tissue and the vegetation including several with a Maltese cross configuration consistent with starch grains *(arrow)* (Original magnification ×189)

embolic episode and evaluation is requested to determine whether there is residual thrombotic material on the prosthesis In the extensive series of Roberts and associates[7] of necropsies in patients dying with prosthetic valves after two months they found an 80 per cent incidence of thrombi on the valves The majority of these patients had been well anticoagulated *in vivo* In 30 per cent of these patients the thrombi rendered the valve incompetent or stenotic while 20 per cent of patients had clinical evidence of systemic embolism during life Embolic material was found in intramural coronary arteries on histologic section in 9 per cent of patients dying early and in 9 per cent of patients dying late after valve replacement The most common site of emboli to intramural coronary arteries was from the left ventricular papillary muscle

The patient described today had no evidence of valvular dysfunction in the interim between admissions and we do not know how reliably he took his anticoagulant medication if at all He could very well have had bland thrombus originating on the valvular apparatus which broke off propagating directly or embolizing to occlude one or more coronary orifices

What about the possibility of endocarditis being the source of the coronary embolus? From the clinical presentation we have no evidence to suggest endocarditis of the prosthetic valve except for one extremely important piece of information and that is that the patient had Candida endocarditis previously Before discussing fungal infection a few general comments about prosthetic valve endocarditis are in order

The incidence of endocarditis is increased in two ways by cardiac surgery (1) the surgery itself the use of intravascular catheters during the postoperative period wound infection and pneumonia all increase the possibility of bacteremia and subsequent endocarditis and (2) immediately following surgery and perhaps permanently the patient has a susceptible focus for infection because of the prosthetic valve which is a foreign body With the advent of large scale prosthetic valvular replacements a new disease prosthetic valve endocarditis has arisen It occurs in 2 to 4 per cent of patients with plastic valves and rarely in patients with tissue valves[8-11] Prosthetic valve endocarditis is usually a devastating complication of valve replacement Two distinct groups of patients become apparent in the interval between the insertion of a prosthetic valve and the onset of clinical infection Endocarditis that develops shortly after surgery is in some instances due to endogenous organisms



Fig 3 This photograph of the base of the heart *reveals* the prosthetic Capetown valve *at the upper right* No vegetative material is apparent on the valve struts or poppet Vegetation was present adherent to the valve ring which cannot be seen in this view The left coronary artery *(LCA)* has been opened longitudinally for approximately 1 5 cm Beyond this point the vessel was cross ectioned *Between the two arrows* at the level of the *bifurcation of the left main coronary into the left anterior descending and left circumflex branches the vessel is completely occluded by a recent embolus*

However the majority of the cases appear to be due to contamination from personnel operating room air or pump equipment Two thirds of individuals subjected to cardiac surgery were found to have agglutinating antibodies to Candida species 10 to 13 days after operation [2] Pneumonia uncontrolled bacterial endocarditis wound and urinary tract infections have often been the source of organisms colonizing prosthetic valves after implantation [1] Prognosis for recovery is poor when intracardiac infection occurs early after operation with the fatality rate exceeding 80 per cent despite administration of potent antibiotics and surgical intervention [7] The clinical course of valvular infection that occurs late after prosthetic valve insertion allegedly is said to have a better prognosis probably related to successful suppression of transient bacteremias associated with urinary or dental manipulations Except in anecdotal cases true endocarditis of prosthetic valves is usually unresponsive to medical therapy requiring surgical replacement with a high associated mortality rate The major reason for the poor prognosis relates to the fact that infection often resides behind the site of attachment of the prosthesis and antibiotics penetrate into this area with difficulty [7]

Endocarditis involving the aortic valve prosthesis is usually seen in patients who are qui sick Although peripheral emboli may be the first manifestation of infection the patients usual present with severe aortic regurgitation high fevers and ECG evidence of conduction tre involvement Indeed almost all cases of bacteria endocarditis seen in patients with prosthetic valves are complicated by ring abscesses wit invasion of conduction tissue [8,11]

Certainly the patient we are discussing toda did not manifest signs of endocarditis early af his surgery and there was nothing to suggest th diagnosis in the interim prior to his final adm sion One note about Candida endocard though There is a high incidence of recurre Candida infection on prosthetic valves even af a long postoperative antibiotic course [1,3] M times the prosthetic valve must be removed a replaced with a new one Some have eve suggested that in right sided fungal endocardit the valve should be removed and not replaced until one is sure all traces of fungal infection have been eliminated

Could the patient have had a recurrence of h initial Candida endocarditis four months late with a terminal embolic event in the corona

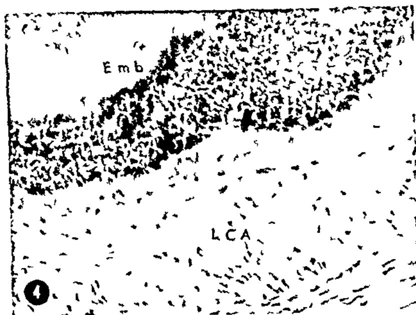


Fig 4 A section of the left coronary artery *(LCA)* from the level of the vessel occluded by embolus *(Emb)* The vessel wall has no evidence of atherosclerosis The lumen is completely filled with material identical to the vegetation observed on the native aortic valve seen in *Fig 1* Similar material was found adherent to the prosthetic valve ring Note the absence of reaction in the underlying vessel wall (PAS stain original magnification ×189)

arteries? Could the infection have been smoldering without systemic evidence for endocarditis? Based on the information provided in the protocol I can t be sure Of course it is also possible that he continued his intravenous drug use and subsequently developed a new infection

In conclusion I must admit that I m caught on a knife edge between ascribing this man s death to a myocardial infarction secondary to a thrombus originating about the area of the prosthetic valve or the faint possibility of an embolus from a silent recurrent endocarditic process Being a fan of major league baseball I would have to play the averages and guess an embolus from a prosthetic thrombus was the cause of this man s myocardial infarction and untimely death However I cannot discount the possibility of recurrent Candida endocarditis with a coronary embolus as its initial and final manifestation

Dr Frishman s diagnosis

1 Coronary embolus from prosthetic valve thrombus

2 ? Recurrent Candida endocarditis

Dr Factor I would like to begin my discussion of the pathological findings by reviewing the aortic valve specimen surgically removed four months prior to death

The valve was submitted in fragments and was markedly fibrotic and focally calcified consistent with prior damage Active fibroblastic proliferation and chronic inflammation were present within the valve tissues On the surface several large vegetations were seen composed predominantly of yeast having features compatible with Candida species (Fig 1) Numerous PAS and silver methenamine positive pseudohyphae appeared to be proliferating within an amorphous eosinophilic proteinaceous material Focally extension of pseudohyphae into the underlying valve tissue was observed however the organism appeared to be of relatively low virulence as judged by the degree of tissue invasion and the paucity of inflammation This may of course be a result of anti fungal therapy that the patient received prior to surgery Gram stained sections of the valve and vegetations failed to reveal the presence of bacterial organisms

One interesting finding which to my knowledge is the first time that such an observation has been made in a case of addiction and endocarditis was the presence of birefringent material having features of talc and starch within the monilial vegetation and the underlying reactive valvular tissue (Fig 2) Several birefringent granules can

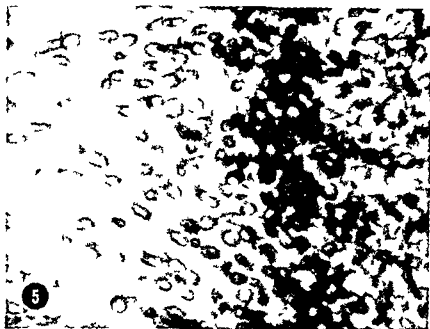


Fig 5 A high magnification of the coronary artery embolus reveals numerous budding yeast and pseudohyphae typical of Candida species The same morphology was noted with material removed from the prosthetic valve ring as well as from the vegetation adherent to the native aortic valve excised surgically (PAS stain original magnification ×1200)

be seen with a Maltese cross configuration, typical of starch grains These grains were also found to be PAS positive This foreign material, of the sort frequently associated with intravenous drug addiction, within the vegetation and valve substance may be directly related to the pathogenesis of this patient's endocarditis It is conceivable that the foreign particles directly damaged the valve surface leading to the deposition of fibrin and platelets which subsequently became colonized by circulating bacteria and yeast It is also possible however that the particulate emboli lodged on a previously existing vegetation At the very least however their presence in the surgical specimen tells us that the patient had continued his intravenous injections even though he allegedly was on methadone maintenance for 6 years

Talc starch and other birefringent foreign body granulomas have been described most frequently in the lungs of intravenous drug users[12, ,] where they occasionally may lead to pulmonary hypertension[12,] This material has also been observed in the skin and subcutaneous tissue of skin poppers and in the walls of veins and lymphatics Clearly however in some circumstances the particulate matter may cross the pulmonary vascular bed and be found in systemic circulation Granulomas have b described in retinal capillaries,[15] liver spleen[17] and kidneys[17] In the case we are disc ing the presence of this material on the ao valve means that it must have crossed the l capillaries to have reached the systemic circu tion Judging by the descriptions in the literat that I have cited this is not that rare howe finding this material on the valve is a uni occurrence

The autopsy was performed 12 hours after patient s death and served to confirm many Dr Frishman s diagnostic impressions The he weighed 570 grams and showed evidence of pr surgical manipulation On opening the aorta fr the ascending segment down to the prosthe Capetown valve the valve was seen to be situ properly with all sutures intact and with evidence of paravalvular leak or poppet dysfun tion On the cloth covered ring and on the c ends of the anchoring sutures small friable ta vegetations were observed appearing somewh different from the usual fibrin and platelet no bacterial thrombi Upon opening the corona arteries longitudinally they were found to remarkably free from atherosclerosis However

the left coronary artery just at its bifurcation into left anterior descending and left circumflex branches an occluding embolus was impacted in the lumen having a gross appearance identical to the vegetative material on the prosthetic valve (Fig 3)

Histological sections of the vegetations and the embolus revealed the presence of PAS positive budding yeast and pseudohyphae identical to those observed four months previously and again consistent with Candida species (Figs 4 and 5) No reaction in the coronary artery wall was noted attesting to the acuteness of the embolus Multiple sections of the myocardium and the native aortic valve fibrous ring failed to reveal any evidence of invasion and/or embolization by the yeast The myocardium had focal hyper eosinophilic fibers and contraction bands consistent with acute ischemia Additionally there were foci of chronic inflammatory cells typical of the Bracht Wachler bodies associated with chronic endocarditis

The remainder of the general autopsy revealed changes compatible with cardiogenic shock such as pulmonary edema and visceral congestion Other findings included a 2 400 gram liver with histologic evidence of fibrosis and chronic active hepatitis This serves to remind us of the frequency of hepatic abnormalities in intravenous drug users [8] Additionally we found a focal splenic infarction but we could not demonstrate the presence of yeast The kidneys had no striking morphological changes Unfortunately permission to examine the brain was not granted so we could not confirm the clinical impression of a cerebral embolus

Of interest polarizing microscopy of the prosthetic valve vegetations and the coronary embolus failed to reveal any positive birefringent material Additionally a study of the lungs liver spleen and kidneys was negative for any talc or starch granules Therefore the presence of birefringent material was limited to the vegetation and native aortic valve removed surgically four months prior to death

So in summary this patient had an acute Candida embolus to the left coronary artery arising from clinically silent yeast vegetations adhering to the prosthetic ring A similar case of coronary embolus secondary to recurrent Candidiasis has been described one month following aortic valve replacement in a drug addict [11] However the absence of any clinical signs or symptoms of recurrent endocarditis for the four months following surgery is another unusual feature of the case discussed today We cannot be certain if the embolus resulted from recurrent Candidiasis or from a new infection secondary to continued drug abuse I would favor the former view because of the relative lack of proliferation of the organism which I think is a result of the amphotericin B therapy It is more likely that a newly introduced organism following cessation of chemotherapy would be more apt to demonstrate tissue invasiveness

Although Dr Frishman played the baseball averages to reach his diagnosis I would like to suggest that the averages may be correct but that the game may be wrong I think that in light of a single large Candida embolus landing in the proximal left coronary artery and nowhere else systematically that the result is more analogous to a hole in one Therefore the game in this case should be changed to golf

Final Diagnosis

1 Recurrent Candida endocarditis of prosthetic aortic valve

2 Acute Candida embolus to left coronary artery

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Fundamentals of clinical cardiology

Approach to the management of unstable angina

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> To dogmatize on questions of medical practice is to invite controversy and tempt disaster
>
> Samuel Hopkins Adams
> (1871 1958)
> *The Health Master* Introductory Note

At the present time controversy exists concerning the definition natural history and management of unstable angina The literature abounds with articles extolling the virtues of urgent coronary bypass surgery for this clinical syndrome[1-3] while other articles plead for conservative medical management[14-16] Several excellent reviews have appeared in the literature summarizing the studies prior to 1976[17-19] Unfortunately due to the lack of precise clinical definition and arteriographic and ventriculographic correlations these early studies have not resolved the controversy

The practicing physician has a dilemma He has to make a decision with respect to therapy when confronted with the patient presenting with unstable angina The major goals of therapy include relief of pain during the acute episode prevention of subsequent episodes of unstable angina prevention of myocardial infarction and prolongation of life Emergency coronary bypass surgery has been advocated by many as the treatment of choice for patients with unstable angina[1] Is the physician remiss if he does not recommend urgent arteriography and bypass surgery for his patient? What are the alternatives? This discussion will describe an approach to the management of the patient with unstable angina and attempt to justify the rationality of that approach based on the literature and personal experience

Terminology

There are many terms that have been used in the past to describe the syndrome or syndromes intermediate between chronic stable angina pectoris of effort and acute myocardial infarction[20] Whenever ideas fail men invent words[21] Terms that have been used include coronary failure[22] impending myocardial infarction[23] acute coronary insufficiency[24] intermediate coronary syndrome[25] preinfarction angina[26] status anginosus[27] unstable angina[28] crescendo angina[29] and accelerated angina pectoris In the literature the one year mortality rate for patients with this syndrome treated medically has been reported to vary from 3 to 60 per cent and the myocardial infarction rate has varied from 0 to 91 per cent[3, 16, 30-3]

The multiplicity of terms and definitions in the literature has led to much confusion over natural history and treatment comparisons Unstable angina has become the currently preferred term connoting the instability of the clinical situation However to merely label the patient as having unstable angina ignores the fact that patients who present with unstable angina are not a homogenous group

Classification

In terms of clinical symptoms and signs coronary anatomy ventricular function response to therapy and prognosis there is a wide spectrum of findings in the population labeled unstable angina In developing guidelines for management the clinician must integrate these factors

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normal coronary arteries have been found in 6 to 14 per cent and left main coronary disease has been found in 4 to 20 per cent[41] Patients with normal or near normal coronary arteries are reported to have an excellent survival[4] while patients with left main disease tend to do poorly with medical treatment[7, 8] With this wide spectrum of coronary anatomy it is not surprising that there is wide variability in prognosis

There also is a wide spectrum of ventricular function Of our 200 consecutive patients an ejection fraction above 50 per cent was found in 75 per cent ejection fractions between 30 to 50 per cent were found in 18 per cent and ejection fraction below 30 per cent was seen in 7 per cent

5 *Operability* Not all patients with unstable angina are operable In the literature operability has been arbitrarily defined as follows

1 Greater than 70 per cent reduction in lumen diameter of a major proximal coronary artery

2 A patent coronary artery distal to the obstruction with a diameter greater than 1.5 mm and

3 Acceptable left ventricular performance defined as an ejection fraction greater than 30 per cent and a left ventricular end diastolic volume less than 125c c /M

Of 200 patients we studied 81 per cent were considered operable and 19 per cent were considered inoperable (7 per cent due to poor left ventricular function 4 per cent due to poor distal vessels 8 per cent due to insignificant coronary disease)

Dr C Richard Conti and I recently reported on 32 patients with unstable angina treated medically and followed up for an average of 48 months[5] Mortality rate was 9 5 per cent in 21 patients considered operable as contrasted to 35 per cent of 11 patients considered inoperable due to poor left ventricular function and/or poor distal vessels Although the prognosis is poor in patients considered inoperable the therapeutic possibilities are limited

Management of the individual patient can best be directed and a prognostic statement about that individual can most accurately be made if all factors listed in Table I are known Before reviewing the management of the individual with unstable angina it is appropriate to review known and hypothesized mechanisms involved in the pathogenesis of unstable angina

Table II Approach to management of the patient with unstable angina

A	CCU admission
B	Search for treatable causes
C	Document objective evidence of ischemia
D	*Intensive individualized pharmacologic therapy*
E	Evaluate response to therapy
F	Symptoms refractory — (urgent surgery if feasible)
G	Symptoms improved — (continued medical therapy in the majority)

Pathophysiology of unstable angina Anginal syndromes are the clinical manifestation of myocardial ischemia in which myocardial oxygen supply is unable to meet the myocardial demand for oxygen This imbalance may be due to (a) increased demands with a fixed supply (b) fixed demands with decreased supply or (c) a combination of these factors

The major determinants of myocardial oxygen demand include heart rate contractility and wall tension which is primarily dependent on ventricular volume and pressure[50, 51] Since oxygen extraction is at or near maximal in the normal coronary circulation increased oxygen supply is dependent on increased coronary flow When there is *significant obstruction of a coronary* artery the capacity for increased flow and hence increased oxygen supply is limited

Why does angina become unstable ? The mechanisms are not entirely clear and may be multifactorial[52, 53] The mechanism of episodes of angina of effort is at least in part related to increased myocardial oxygen demand The mechanism of episodes of angina occurring at rest appears related to decreased myocardial oxygen supply[5, 7] Decreased supply may be caused by *progression of coronary atherosclerotic* disease to a critical narrowing transient coronary artery spasm[5, 57] rupture of atheromatous plaques[58] transient platelet plugging or combinations of these factors

Maseri and associates[55, 7] have recently reported evidence that supports the postulate that at least in some patients angina at rest is caused by a primary reduction of myocardial blood flow[5, 5] In a group of closely monitored patients with recurrent rest pain a decrease in coronary vein oxygen saturation preceding the ischemic episode was found in the absence of a rise in the determinants of myocardial oxygen demands

addition, thallium 201 imaging performed during ischemic episodes in patients with rest pain with either transient ST segment depression or elevation demonstrated deficits suggesting a reduction in myocardial blood flow at that time [57] Coronary artery spasm occurring in the presence or absence of fixed coronary disease has been recently emphasized in the literature as an etiologic factor in the occurrence of angina at rest [59, 60] How common this mechanism is remains to be determined

Approach to management of unstable angina

The major consequences of ischemia are sudden death life threatening arrhythmias myocardial infarction and pain The patient with unstable angina has frequent or prolonged ischemia The goal of therapy therefore is to treat and prevent ischemia in an attempt to prevent death and myocardial infarction and to relieve pain An appropriately aggressive' approach to the management of unstable angina is outlined in Table II Therapy must be individualized and is aimed at maintaining coronary blood flow while reducing myocardial oxygen demands

A CCU admission It is generally agreed that most patients with crescendo angina or recent onset rest pain should be hospitalized in the protective environment of a coronary care unit to rule out an evolving myocardial infarction and to provide continuous monitoring and prompt treatment of life threatening arrhythmias [11] However some patients react adversely to the CCU environment and are best managed elsewhere in the hospital or in a secure home environment There is not universal agreement on the need for hospitalization of the patient in the subgroup of recent onset angina of effort [11] There is little data on the subgroup The Edinburgh study suggests a relatively low 6 month mortality and myocardial infarction rate despite the fact that the vast majority of these patients were not hospitalized [18] In those patients with prolonged pain (greater than 10 to 20 minutes) marked ECG changes or a crescendo pattern hospitalization appears warranted

Once the patient is admitted to the CCU serial ECG s and enzymes (especially MB CPK isoenzyme if available) should be obtained to exclude a recent MI It is prudent to treat these patients in much the same manner as one treats patients with relatively small uncomplicated myocardial infarctions Indeed there may be necrosis of tissue but of insufficient amount to be detected by tests presently in clinical use

In the CCU a major emphasis is on reduction of the determinants of oxygen demand A patient who is anxious may be tachycardiac hypertensive and have high levels of circulating catecholamines Unstable angina 'is the one condition among all others in which the patient may literally scare himself to death [61] The physician should aim for emotional as well as physical rest Bed rest reassurance and sedation may go a long way in reducing the determinants of myocardial oxygen demand Reassurance by the physician and CCU personnel may have a calming effect on the patient and may be even more important than bed rest and sedation [61]

Search for treatable causes A major endeavor should be to find an aggravating or precipitating factor that is amenable to treatment Conditions such as unrecognized paroxysmal arrhythmias anemia hypertension thyrotoxicosis emotional stress or use of sympathomimetic drugs should be searched for and appropriately treated [61] These can be easily overlooked and failure to recognize them may result in prolonged hazardous and sometimes unnecessary treatment

C Document objective evidence of ischemia One should make an attempt to document objective evidence of ischemia especially if the chest pain is not typical Abnormal physical findings before during or after an ischemic episode may include an increased arterial pressure and heart rate a fourth heart sound gallop an abnormal precordial bulge or the murmur of papillary muscle dysfunction Even more valuable is an ECG taken during pain The ECG may show transient ST segment shifts or T wave changes that revert to baseline as the pain abates confirming the clinical impression of ischemia as the cause of the patient s chest pain We have found that the direction of the transient ST segment shift is of neither diagnostic nor prognostic value The coronary anatomy left ventricular function and long term prognosis do not appear to differ in those patients with unstable angina who manifest transient ST segment elevation compared to patients with transient ST segment depression [4] However in patients with simultaneous ST shifts in both the anterior and inferior leads the index of suspicion of left main coronary disease increases

Patients who do not manifest any objective

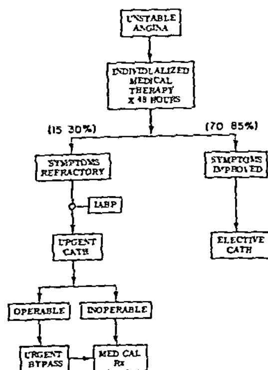
evidence of ischemia while at rest in the coronary care unit should receive the same initial therapy as patients who manifest objective changes However patients without objective signs of ischemia should be strongly considered for future stress testing if the etiology of the chest pain syndrome remains in doubt [62]

D **Intensive pharmacologic therapy** The cornerstones of pharmacologic therapy are nitrates and beta blocking agents The pharmacologic basis of their therapeutic action has been recently reviewed by Sostman and Langou [63] In unstable angina patients one should not only treat each individual pain episode after it occurs but also treat aggressively in an attempt to prevent further ischemic episodes [6]

Nitrates Sublingual nitroglycerin is usually adequate to relieve isolated episodes of pain If the episode of pain does not respond to 0 8 to 1 6 mgm of nitroglycerin given over 10 to 20 minutes parenteral analgesics such as morphine or meperidine are indicated. In addition long acting nitrates should be started promptly soon after admission to the CCU The desired effects are to reduce ventricular volume by peripheral venous pooling and to decrease arterial pressure by systemic arteriolar dilatation without a reduction in coronary blood flow [65] There is also evidence that nitrates may improve the distribution of coronary blood flow to the endocardium and may enhance the electrical stability of acutely ischemic myocardium [66] In the event coronary artery spasm is playing a major role in the pathogenesis of the ischemia the coronary vasodilatory effect of the nitrates may be beneficial It is usually most convenient to give long acting nitrates in the form of high dose oral nitrates (20 to 50 mg) or in the form of 2 per cent nitroglycerine ointment applied to the skin in increments of one half inch Oral and cutaneous nitrates appear to have beneficial hemodynamic effects persisting for up to 4 to six hours [6] If used sublingual preparations of isosorbide dinitrate or chewable erythrityl tetranitrate should be given as often as every 1½ to 2 hours as their effect is probably dissipated during that time Nitrates have the potential hazard of decreasing markedly the ventricular filling pressure in patients with poorly functioning ventricles and thereby decreasing cardiac output However with careful titration nitrates will actually increase cardiac output in most patients An occasional patient may become significantly hypotensive and bradycardic after starting nitrates This idiosyncratic reaction can be treated by leg raising (allowing the blood that is pooled in the periphery to return centrally) and only rarely requires the addition of atropine

Propranolol In 1973 Fischl and colleagues[11] demonstrated that the beta adrenergic blocking agent propranolol appeared to be an effective and safe therapy in preventing the recurrence of pain in 17 of 20 patients with unstable angina Propranolol is thought to exert its beneficial effect by reducing heart rate arterial blood pressure and myocardial contractility with a resultant decrease in myocardial oxygen demand [63] Propranolol appears extremely effective in reducing the recurrence of pain episodes although its effect on the natural history of patients with angina is unclear Of 100 consecutive patients with unstable angina treated with propranolol at The Johns Hopkins Hospital and Baltimore Veterans Administration Hospital 80 per cent have had a prompt decrease in the frequency of pain episodes with lowering of heart rate and blood pressure [5] There is marked variability among patients in the effective blood level of propranolol after a single orally administered dose [1] In addition there is marked individual variation in response to the action of propranolol Thus we have found it useful to begin therapy with a 10 to 20 mg dose and double the dose every 6 hours until there is a therapeutic response or side effects occur The goal of propranolol therapy is to blunt the heart rate response to anxiety or exertion Previous recommendations were to reduce the resting heart rate below 60 We no longer use a minimum *resting* heart rate to dictate a maximum dose of beta blockade but continue to increase the dose until pain is controlled or the patient is symptomatic due to hypotension bradycardia fatigue or CHF The maximum dose required in our population has varied from 40 to 1 200 mg /day

Propranolol is contraindicated in patients with bronchospasm in patients on monoamine oxidase inhibitors and in patients with uncontrolled congestive heart failure not related to tachyarrhythmias [6] Propranolol can be used safely in the presence of mild left heart failure [33] but careful observation is imperative Propranolol should be used with caution in patients with diabetes mellitus because symptoms of hypoglycemia may be masked and insulin requirements may be



Fg 1 Timing of catheterization dependent upon response of symptoms to therapy and management of patients with refractory symptoms. Abbreviations *IABP* = intra aortic balloon pump.

altered[63] The role of intravenous propranolol remains to be determined but it may be useful in patients who cannot take oral medications

Although "nature, time and patience are the 3 great physicians [3] it is important to treat these patients with a sense of urgency Until symptoms are controlled dosages of medication are rapidly increased watching closely for limiting side effects.

Digitalis may be needed to prevent or treat early congestive heart failure In patients with stable angina digitalis and propranolol have been shown to be a highly useful combination [73] Antiarrhythmic drugs should be employed to supplement the antiarrhythmic effects of pro pranolol in patients with life threatening ar rhythmias

Combination therapy with long acting nitrates and propranolol has additive value in controlling the determinants of myocardial oxygen demand The tachycardia which may develop with nitrates can be prevented by appropriate doses of beta blockers.

Even in the absence of recurrent pain these medications should be continued for at least one week Myocardial ischemia or ischemic left ventricular dysfunction may occur in the absence of chest pain [74] If reduction or discontinuation of therapy is undertaken this should be done in a slow titrated fashion to avoid any possible rebound symptoms [75] Should coronary bypass surgery be contemplated recent reports suggest that propranolol dosage need not be significantly altered prior to bypass surgery [*]

Anticoagulation Although the early literature is replete with references extolling the benefits of anticoagulants [34 35 77 81] and anticoagulant drugs are given to many patients the value of therapy with either heparin or warfarin sodium remains controversial. Early studies suggest impressive benefit from anticoagulation [3 3 * *] but these studies were poorly controlled and their conclusions must be questioned While awaiting a well designed and properly controlled clinical trial, we employ anticoagulants if there are no clinical contraindications. Low dose subcutaneous heparin therapy has fewer side effects than full-dose heparin therapy but has not been documented to be efficacious in the clinical setting of unstable angina

E Evaluate response to therapy What per centage of patients hospitalized for unstable angi na will become asymptomatic or nearly so within 48 hours of hospitalization? Have recent advances in medical therapy decreased the likelihood of persistent symptoms? It is instructive to compare the study of Gazes and colleagues (1960 s treatment) with that of Stoner and Harrison[7] (197 treatment) Gazes maximum therapy (bed rest sedation analgesia nitrates and anticoagulants in the majority) yielded a 61 per cent response rate while Stoner and Harrison found that despite the addition of propranolol the response rate was only slightly better (70 per cent) As noted before patients in whom symptoms persist beyond the first 48 hours of hospitalization have a much worse prognosis than those who respond

Rapid stepwise increments in propranolol dosage may yield slightly better results Fischl and associates[1] utilized this approach to control unstable angina symptoms in 17 of 20 patients (85 per cent) with relief from recurrent pain being rapid usually within 12 hours Of note seven of these patients (35 per cent) had subsequent breakthrough of pain but each was controlled by further increases in propranolol dosage

As shown schematically in Fig 1 it appears that with appropriate intensive medical therapy approximately 70 to 85 per cent of patients will

adequately controlled while 15 to 30 per cent will continue to have recurrent pain in the CCU The former group of patients have a relatively good prognosis while the latter patients with recurrent pain are at high risk for development of myocardial infarction and death

F Symptoms–refractory There is little disagreement about the management of the 15 to 30 per cent of patients who continue to have recurrent severe chest pain episodes despite vigorous medical management In most of these patients the continuing symptoms can be reversed by successful coronary bypass surgery Surgery has been reported to have a dramatic effect in eliminating or improving symptoms in 65 to 90 per cent of patients[18 1 6 83]

For patients with recurrent episodes of angina the clinician should review the management and document that medical therapy has been appropriate and really is *maximal* If the therapy has been maximal the patient is considered a medical failure At this time the patient should undergo cardiac catheterization and if his condition is found to be operable he should undergo coronary bypass surgery The criteria for operability become less rigid in these patients who have been found to be refractory to medical therapy

Consideration should be given to using the intra aortic balloon pump (IABP) to provide circulatory support while cardiac catheterization and surgery are undertaken In recent reports the use of the IABP has been very successful in controlling ischemic symptoms in refractory patients and may transiently turn off the patient s pain episodes[64 67] However this approach is not without risk and cannot be used in some patients[87] The technique is not suitable for patients with major peripheral arterial disease When the IABP can be employed coronary arteriography and induction of anesthesia for surgery can be more easily and probably more safely performed[8]

The inoperable refractory patient has a grave prognosis In addition to continuing and optimizing the medical therapy the clinican can only offer support and symptomatic relief with analgesics as needed If the inoperable patient has responded to the IABP the weaning process makes a difficult clinical situation even more difficult

Newer forms of therapy are presently undergoing evaluation These include systemic arteriolar dilators[8] (especially if there is elevated arterial pressure and/or increased left ventricular filling pressure) antiplatelet therapy[92] fibrinolytic agents[9] and coronary vasodilators including nifedipene[91] and verapamil[9] Hultgren[2] suggests that nitroprusside infusion might be useful in patients with persistent pain left ventricular failure or hypertension not responsive to the usual therapeutic measure It is possible that the addition of some of these newer therapies either alone or in combination will allow us to convert some or all of the medical failure patients into responders

G Symptoms–improved Controversy exists concerning the subsequent evaluation and management of the majority of patients with unstable angina who initially respond to medical therapy Claims have been made that urgent bypass surgery should be performed in an attempt to prolong life and to prevent myocardial infarction[1] Unequivocal evidence for this in patients with unstable angina is presently lacking Several recent prospective randomized trials have compared urgent coronary bypass surgery to initial vigorous medical management in patients with unstable angina[49 93 95] (Table III) These studies are biased in that only operable patients were included and patients who failed on intensive medical regimens were excluded

Nevertheless these studies have demonstrated in this population of patients with unstable angina that

1 Intensive medical therapy is associated with a low in hospital mortality and morbidity rate

2 Urgent surgery does little to improve immediate survival or MI rate

3 The long term survival and myocardial infarction rate are not worsened by initial medical treatment

The mortality and morbidity of coronary bypass surgery is generally recognized to be higher in patients with unstable angina than in patients with stable angina In the recent literature the incidence of perioperative myocardial infarction varies from 4 to 25 per cent (average 10 per cent) and the surgical mortality rate varies from 0 to 28 per cent (average 8 per cent) for unstable angina patients[1 13 3 33 96 97] At the Johns Hopkins Hospital the surgical mortality rate for patients with unstable angina in the first half of 1978 was 4 7 per cent compared to that of less than 2 per cent for patients with stable angina

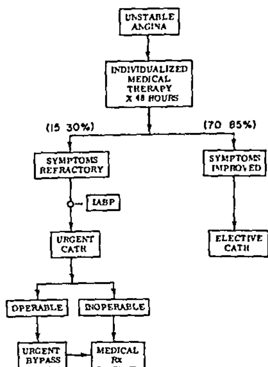


Fig 1 Timing of catheterization dependent upon response of symptoms to therapy and management of patients with refractory symptoms. Abbreviations *IABP* = intra aortic balloon pump

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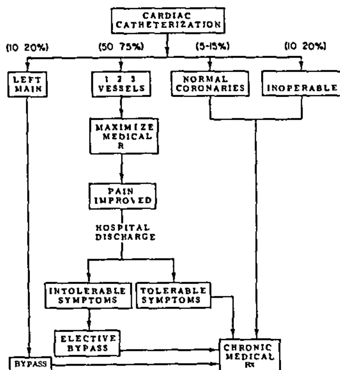


Fig 2 Medical and surgical management of unstable angina dependent upon catheterization findings and symptoms.

surgery although most will remain on chronic medical therapy adjusted according to their symptomatology

Although the information obtained from cathe terization is helpful and my prejudice is that most patients should be catheterized the recom mendation for catheterization must be individu alized For the patient who is elderly who would otherwise not be considered a surgical candidate who has had an isolated episode of pain without recurrence catheterization need not be done

Further considerations

Role of stress testing In those patients in whom the diagnosis remains uncertain stress testing should be performed in an attempt to document objective evidence of ischemia An atrial pacing stress test is probably safer than the treadmill stress test in the unstable patient [3] Among our patients with unstable angina who have undergone atrial pacing stress tests during cardiac catheterization there were no complica tions as a result of the pacing induced tachycar dia The sensitivity and specificity of atrial pacing for the detection of ischemia in this syndrome are unknown but possibly can be improved when combined with thallium scanning techniques [1] If the atrial pacing test is negative a treadmill stress test may be warranted

In those patients who respond to medical ther apy a limited treadmill stress test prior to hospi tal discharge is helpful The work load should be roughly equivalent to the amount of activity that the physician will recommend the patient perform while convalescing at home One can then objectively see that the patient can tolerate such activity If the patient develops early and marked ischemia with minimal exertion a more prolonged convalescence might be recommended Unstable angina should not be considered as an absolute contraindication to appropriately graded stress testing [105]

Follow up Serial stress testing can also be used during outpatient follow up to evaluate the response to therapy and to best determine safe levels of exertion [3] A carefully graded program of exercise training may be beneficial in improving the patient s functional capacity and sense of well being [106] Attention should be given to long term risk factor control Smoking should be discontinued and hypertension and weight should be controlled [1,7] Conscientious control of these

Table III Prospective randomized studies of unstable angina

Ref No	*Rx*	*Pts*	*Hospital*		*Late*		*Class III IV angina*	*Follow up*
			Death	*MI*	*Death*	*MI*		
95	Med	147	3%	7%	6%	10%	45%	24 months
	Surg	141	5%	17%	5%	11%	15%	
93	Med	19	0	0	0	11%	63%	4 months
	Surg	21	5%	14%	0	0	5%	
94	Med	14	0	0	7%	0	38%	18 9 months
	Surg	13	8%	31%	0	0	0	

In the early 1970s it was thought that unstable angina was the primary indication for urgent bypass[1 11] It is now clear that effective medical therapy is available and will cool down the majority of patients with unstable angina Surgery is no longer an emergency and can now be more carefully planned and executed[8] Those who still advocate urgent surgery suggest that delaying surgery in some patients may result in inoperable status[9] The randomized controlled studies to date have not demonstrated that the mortality or MI rate are worsened by initial medical treatment[1 95]

The high incidence of long term late medical failures however suggests that surgery has a definite role to play in the treatment of these patients[93 95] Bypass surgery does not need to be urgent in the majority of patients[9] The role of surgery in unstable angina appears to be similar to that in stable angina i e reduction of pain episodes in operable patients who fail to be adequately controlled by medical treatment

The time of cardiac catheterization depends upon one s philosophy concerning the role of bypass surgery and the patient s response to medical therapy For the patient refractory to medical treatment cardiac catheterization is performed urgently (within 48 hours) For the patient who responds to medical therapy catheterization should be performed electively (between 1 to 6 weeks) (Fig 1)

The information obtained from elective catheterization can be helpful both prognostically and therapeutically (Fig 2) Among the unstable patients those with substantive left main coronary stenosis are thought to have an extremely poor prognosis[4] and clinical clues are not reliable in differentiating this subgroup prior to catheterization[64] Studies have suggested that bypass surgery improves survival in the patien with symptomatic left main stenosis[4 100-101] Th 10 to 20 per cent of patients who are found t have substantive left main stenosis are presentl being offered bypass surgery Whether futur medical therapies (some of which are presentl under investigation) would beneficially affect th natural history of these high risk patients remain to be determined

The 10 to 20 per cent of patients who are trul inoperable due to poor distal vessels or extremel poor left ventricular function also have a poo prognosis They should be maintained on chron medical therapy which should be optimized an continually re evaluated

The 5 to 15 per cent of patients who hav normal or minimally diseased vessels can b reassured that their long term survival in gener is good The role of provocative agents in a attempt to document coronary spasm remains t be determined[102] If objective changes of ischem have been documented spasm can be considere a likely mechanism and therapy should b directed toward preventing recurrent spasm i e employing nitrates and the newer coronar vasodilators In the absence of documented objec tive changes of ischemia one should consider an evaluate for noncardiac etiologies of chest pain

The majority (50 to 75 per cent) of patients a found to have operable single double or tripl vessel disease The clinician s philosophy an prejudices about the role of surgery in stabl angina dictate the course of action for the patients Until convinced otherwise my bias is t maintain these patients on medical therapy bu to offer elective bypass surgery if the patien develops recurrent intolerable symptoms Thu those patients who remain asymptomatic or hav tolerable symptoms will avoid the ordeal

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Clinical pharmacology of the new beta-adrenergic blocking drugs. Part 4. Adverse effects. Choosing a β adrenoreceptor blocker

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The adverse effects of beta adrenoreceptor blocking drugs can be divided into two categories: (1) those that result from known pharmacologic consequences of beta adrenoreceptor blockade and (2) other reactions that do not appear to result from beta adrenoreceptor blockade.

Side effects of the first category are widespread because of the ubiquitous nature of the sympathetic nervous system in the control of physiologic and metabolic function. They include asthma, heart failure, hypoglycemia, bradycardia and heart block, intermittent claudication, and Raynaud's phenomenon. The incidence of these adverse effects varies with the type of beta blocker used.

Side effects of the second category are rare and include an unusual oculomucocutaneous reaction and the possibility of carcinogenesis.

Major clinical trials

There have been extensive clinical trials identifying the nature and frequency of side effects with beta blocking agents. The Boston Collaborative Drug Surveillance Program dealt with propranolol in 800 hospitalized patients and with practolol in 199 patients.[1] Forrest reported on adverse reactions to oxprenolol among 4,400 patients receiving the drug for angina. Two large trials have been carried out with pindolol which detailed at length the types and frequency of side effects with this drug.[3, 4]

In the Boston Collaborative Drug Surveillance Program, propranolol was used for mixed clinical indications and adverse reactions attributable to propranolol were reported in 79 patients (9.9 per cent). These are summarized in Table I. Ten adverse reactions were considered life threatening and all appeared to result from impairment of cardiac function. Of the 69 other reactions, 43 of these also involved interference with cardiac performance but were not life threatening.

The frequency of side effects was independent of the dose used. Reactions were more common among older patients and those with azotemia.

In the same study of the 199 patients who received practolol (cardioselective), adverse reactions were reported in 18 (9.0 per cent). The nature and frequency of adverse reactions to practolol resembled those of propranolol (Table II). In the studies of oxprenolol[2] and pindolol,[3] similar findings were also noted.

Over all, the frequency of side effects among the beta blockers is similar. Whether the newer

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e I Adverse reactions to propranolol among 800 hospitalized medical patients*

Severity	*Nature of reaction*	*Number of pts*	*%*
Life-threatening	Shock	5	0 6
	Bradycardia and angina	1	0 1
	Pulmonary edema	3	0 4
	Complete heart block	1	0 1
	Total	10	1.3
Non life-threatening	Bradycardia	17	2.1
	Hypotension†	16	2.0
	Congestive heart failure or fluid retention	9	1 1
	Gastrointestinal disturbances	9	1 1
	Central nervous system disturbances (headache dizziness fatigue tinnitus, blurring of vision paraesthesias depression)	9	1 1
	Bronchospasm	4	0.5
	Sensitivity reactions (rash fever)	3	0 4
	2 1 heart block	1	0 1
	Elevation in serum phenytoin level	1	0 1
	Total	69	8.6
Total with adverse reactions		79	9.9

With bradycardia in 3 cases and congestive heart failure in one
†With syncope in 5 cases.

beta blockers with cardioselectivity and/or sympathetic activity can alter the and severity of these effects will be ussed below It is important to note however much of our knowledge to date concerning side effects is derived from either anecdot reports or from small series of patients

dverse cardiac effects related to blockade

Cardiac failure There are several circumstances in which blockade of beta receptors may cause congestive heart failure in patients (1) in an enlarged heart with impaired myocardial function where excessive sympathetic drive is essential to maintain it on a compensated Starling curve and (2) if the stroke volume is restricted and tachycardia is needed to maintain cardiac output

Considering the factors noted above *any* β blocking drug may be associated with the development of heart failure Furthermore it is possible that an important component of heart failure may be accounted for by increases in peripheral resistance produced by non selective agents (e g propranolol timolol sotalol) Practolol is less likely to produce cardiac decompensation and the hemodynamic effects of newer cardioselective agents in patients with myocardial dysfunction have yet to be determined

It has been claimed that β blockers with intrinsic sympathomimetic activity are less likely to precipitate heart failure However there have been no *in vivo* studies to support this contention and it has been shown that these drugs can precipitate heart failure[7] In the dog transplanted denervated heart preparations β blockers with intrinsic sympathomimetic activity have a positive rather than a negative inotropic effect[8] The clinical significance of this effect is uncertain

In patients with impaired myocardial function who need β blocking agents digitalis and diuretics may be used preferably with drugs having cardioselectivity or intrinsic sympathomimetic activity

Atrioventricular conduction delay and sinus node dysfunction Slowing of the resting heart rate is a normal response to treatment with a β blocking drug without intrinsic sympathomimetic activity Healthy individuals can sustain a heart rate of 50 without disability unless there is clinical evidence for heart failure Drugs with intrinsic sympathomimetic activity do not lower the resting heart rate to the same degree as propranolol however all beta blocking drugs are contraindicated (unless an artificial pacemaker is

Table II Adverse reactions to practolol among 199 hospitalized medical patients

Severity	Nature of reaction	Number of pts	%
Life threatening	Pulmonary edema	1	0.5
	Complete heart block bradycardia and shock	1	0.5
	Second degree heart block and hypotension	1	0.5
	Total	3	1.5
Non life threatening	Congestive heart failure	3	1.5
	Bradycardia	4	2.0
	Central nervous system disturbances (dizziness confusion)	3	1.5
	Sensitivity reactions (rash)	2	1.0
	Hypotension	1	0.5
	Gastrointestinal disturbances	1	0.5
	Dyspnea	1	0.5
	Total	15	7.5
Total with adverse reactions		18	9.0

present) in patients with the sick sinus syndrome

If there is a partial or complete atrioventricular conduction defect use of beta blocking drugs may lead to a serious bradyarrhythmia [9] The risk of atrioventricular impairment is not the same with all β blockers Giudicelli and colleagues[10] showed that in dogs it is β blockade and not membrane stabilizing activity which is responsible for atrioventricular conduction impairment Compounds like pindolol or practolol which have intrinsic sympathomimetic activity in dosages producing β blockade do not impair atrioventricular conduction [10]

Beta blocker withdrawal Following the abrupt cessation of beta blocker therapy after chronic administration exacerbation of angina pectoris and in some cases myocardial infarction have been reported [11 13]

Two double blind randomized trials confirmed the reality of a propranolol withdrawal syndrome [3] The mechanism for the propranolol withdrawal effect is unclear and may be related to the multifactorial actions of the drug Reduced exercise tolerance following abrupt withdrawal of chronic propranolol therapy in patients with angina pectoris may be due to loss of sympathetic blockade of cardiovascular function resulting in an acute increase in myocardial oxygen demands Our group demonstrated that abrupt propranolol withdrawal can possibly harm some patients with angina pectoris by also causing rebound platelet hyper aggregability associated with increased anginal frequency decreased exercise tolerance and possible compromise of coronary blood flow [13]

A rebound' effect has not been well defined with the other beta blocking agents However it seems that discontinuation of β blocker therapy should be done gradually and cautiously in patients with ischemic heart disease

Adverse non cardiac side effects related to beta adrenoreceptor blockade

Effect on ventilatory function The bronchodilator effects of catecholamines on the bronchial β adrenoreceptors (β) are prevented by β blockade with non selective agents (e g propranolol) [14]

Comparative studies have shown however that compounds with intrinsic sympathomimetic activity and/or cardioselectivity are less likely to increase airway resistance in asthmatic patients than propranolol [15] Cardioselectivity is not absolute and with higher doses may be lost as has been shown with practolol Since beta selectivity is not absolute a beta $_2$ stimulating agent can be helpful when used concomitantly in patients with bronchospastic disease [18] However in general all beta blockers should be avoided in patients with active bronchospastic disease

Peripheral vascular effects (Raynaud s phenomenon) Cold extremities and absent pulses have been described to occur more frequently in patients receiving β blockers for hypertension compared with methyldopa [19] Among the

blockers the incidence was highest with propranolol and less with drugs having cardioselectivity or intrinsic sympathomimetic activity In some instances vascular compromise has been severe enough to cause cyanosis and impending gangrene This is due to the reduction in cardiac output and blockade of β adrenergic skeletal muscle vasodilation resulting in unopposed alpha adrenoceptor vasoconstriction[21] Beta blocking drugs with cardioselectivity or intrinsic sympathetic activity will not affect peripheral vessels to the same degree as propranolol

Raynaud s phenomenon is one of the undesirable side effects of propranolol treatment[2] [3] It more troublesome with propranolol than practolol probably due to the β blocking properties of propranolol

Patients with peripheral vascular disease who suffer from intermittent claudication often report worsening of the claudication when treated with beta blocking drugs[21] [3] Whether drugs with cardioselectivity in intrinsic sympathomimetic activity can protect against this side effect has yet to be determined

Hypoglycemia Several authors have described severe hypoglycemic reactions during therapy with β adrenergic blocking drugs[6] Some of the patients affected were insulin-dependent diabetics while others were non diabetic Studies of resting normal volunteers have demonstrated that propranolol produces no alteration in blood glucose values[6] although the hyperglycemic response to exercise is blunted

In man mobilization of muscle glycogen is a beta receptor mediated function (β mediated) while mobilization of the liver glycogen depends on alpha receptor stimulation[9] As a result beta receptor blocking drugs (especially non selective beta blockers) may retard recovery from insulin induced hypoglycemia In humans Abramson and associates showed that propranolol delayed the return of blood glucose values to normal after insulin induced hypoglycemia

Likewise if liver glycogen is reduced by fasting or illness the concomitant administration of beta blocking drugs may prolong recovery from hypoglycemia since alternative stores cannot be mobilized

There is also a marked diminution in the manifestations of sympathetic discharge associated with hypoglycemia[3] These findings suggest that propranolol (non cardioselective) interferes with compensatory responses to hypoglycemia and can mask warning signs of this condition This enhancement of insulin induced hypoglycemia may be less with cardioselective agents (where there is no blocking effect on β_2 receptors) and agents with intrinsic sympathomimetic activity (which may stimulate β_2 receptors)[31]

Central nervous system effects Dreams hallucinations insomnia and depression can occur during therapy with the β blockers[**] They are evidence of entry of the drugs into the central nervous system (CNS) and are especially common for the highly lipid soluble β blockers (propranolol alprenolol) which presumably penetrate the CNS better Vivid dreams may also occur with other agents (practolol pindolol) a lesser penetration into the CNS notwithstanding

Severe depression has been described with propranolol therapy especially in patients receiving high doses over long periods of time Oxprenolol which has partial agonist activity was found to have a stimulant rather than a depressant central nervous system action but occasionally it too can cause depression[3]

Clinical pharmacological studies have generally supported the view that β blockers do not have any marked sedative effect No such action could be detected for propranolol sotalol oxprenolol or atenolol[3]

Skeletal muscle effects *In vitro* studies demonstrate that propranolol can produce neuromuscular blockade The direct actions of epinephrine on skeletal muscle are mediated probably through β receptors and tremor is the most common side effect of β_2 stimulating drugs Propranolol has been shown to attenuate the angle jerk and a prolonged curare like effect has been described in one patient[3] Whether the cardioselective β blockers have similar effects remains to be determined

Muscle cramps can occur especially with pindolol and have been described with practolol and propranolol[3] The etiology of this side effect is unknown

Miscellaneous side effects Diarrhea nausea gastric pain constipation and flatulence have been seen occasionally with all beta blockers (2 to 11 per cent of patients)

Hematological reactions are rare rare cases of purpura[38] and agranulocytosis[39] have been described with propranolol

A devastating blood pressure rebound effect has been described in patients who discontinued clonidine while being treated with non selective β blocking agents The mechanism for this may be related to an increase in peripheral resistance [40, 41] Whether cardioselective β blockers have similar effects following clonidine withdrawal remains to be determined

Increase in patient weight may occur Bengtsson noted an average 1 kilogram weight increment in patients taking alprenolol A similar weight gain in patients has also been noted with propranolol [5] pindolol [44] and oxprenolol

Adverse effects unrelated to beta adrenoceptor blockade

Oculomucocutaneous syndrome A characteristic immune reaction—the oculomucocutaneous syndrome—affecting singly or in combination eyes mucous and serous membranes and the skin often in association with a positive antinuclear factor has been reported in patients treated with practolol and has led to the curtailment of its use [45, 5] Close attention has been focused on this syndrome because of fears that other β adrenoreceptor blocking drugs may be associated with this syndrome

The main features in this syndrome in 439 patients reviewed by Nichols were as follows

Eye A gritty feeling in the eye which can progress to a panconjunctivitis keratitis and pannus formation In Nichol s series 18 patients manifested severe eye changes 112 had corneal damage without loss of sight and 146 had eye changes without corneal involvement The average time to develop this syndrome was 23 months after initiating treatment

Skin The skin changes usually begin with a pruritic rash involving the palms and the soles of the feet Thickened plaques which resemble psoriasis may appear Immunofluorescent studies have revealed granular deposits at the dermal–ectodermal junction in some cases

Ear Deafness with serous otitis media has been reported in some patients receiving practolol

Sclerosing peritonitis Thirty three patients with this syndrome were included in Nichol s report Patients may present with colicky abdominal pain or with an abdominal mass This condition may progress in spite of withdrawal of the drug and first develop up to a year after the discontinuation of practolol The peritoneum becomes covered with a film of white fibrous tissue with thicker plaques [46] The natural history of this condition is unknown and the diagnosis has usually been made at laparotomy or autopsy Most patients appear to improve with time after cessation of treatment The mean time of diagnosis of sclerosing peritonitis after starting practolol was 37 months

As with sclerosing peritonitis many of the other practolol reactions are reversible by withdrawal of the drug, together with topical corticosteroids artificial tear solutions antibiotic eye drops and oral corticosteroids

An important consideration is whether the practolol reaction is specific for practolol or is the direct and specific result of pharmacologically induced changes by β blockade [49] There have been few convincing published reports of the oculomucocutaneous reaction with oxprenolol[50, 51] and propranolol [5, 51] For the most part these were specific ocular symptoms and signs without any real evidence to suggest they might reflect an adverse effect to any drug [51]

In view of the extensive and long use of both oxprenolol and propranolol these reactions even if drug induced are exceedingly rare There is need however for vigilance for these reactions during therapy with the newer β blockers

Carcinogenicity Pronethalol the first beta adrenoceptor blocking drug to achieve wide use was withdrawn by its manufacturers because it caused thymic tumors and lymphosarcomata in mice although it did not do so in rats or dogs The doses used to produce these tumors were 10 times the maximum therapeutic concentration

Recently tolamolol and pamatolol two cardioselective beta adrenoreceptor blocking drugs were withdrawn from clinical trials because they caused mammary tumors in mice and rats at high doses

Other beta blockers—alprenolol and practolol—have given some indication of tumorigenicity in rodents [5]

The relevance of these findings to causation of tumors in man is difficult to evaluate the doses were high and the relationship between malignant tumors in animals and man is not defined. A disturbing aspect has been the suggestion that this might be a pharmacologic property of beta

Table III Clinical situations that would influence the choice of a beta blocking drug

Condition	*Choice of beta blocker*
Asthma	Avoid all beta blockers if possible however small doses of cardioselective β blockers (e.g., acebutolol atenolol metoprolol) can be used
Chronic bronchitis with bronchospasm	Cardioselectivity is lost with higher doses Drugs with partial agonist activity (e.g., pindolol alprenolol) can also be used
Congestive heart failure	Drugs with partial agonist activity might have an advantage
Angina	In patients with angina at low heart rates drugs with partial agonist activity probably contraindicated Patients with angina at high heart rates but who have resting bradycardia might benefit from a drug with partial agonist activity
Atrioventricular conduction defects	Beta blockers generally contraindicated but drugs with partial agonist activity can be tried with caution
Bradycardia	β blockers with partial agonist activity have less pulse slowing effect and are preferable
Raynaud's phenomenon Intermittent claudication Cold extremities	Cardioselective agents and those with partial agonist activity might have an advantage
Depression	Avoid propranolol Substitute a beta blocker with partial agonist activity
Diabetes mellitus	Cardioselective agents preferable
Thyrotoxicosis	All agents will control symptoms, but agents without partial agonist activity are preferred
Pheochromocytoma	Avoid all beta blockers unless an alpha blocker is given
Renal failure	Use reduced doses of compounds largely eliminated by renal mechanisms (sotalol, atenolol) and of those drugs whose bioavailability is increased in uremia (propranolol, alprenolol) Also consider possible accumulation of active metabolites (alprenolol propranolol)
Insulin and sulphonylurea use	Danger of hypoglycemia Possibly less using drugs with cardioselectivity
Clonidine	Avoid sotalol (other non selective beta blockers) Severe rebound effect with clonidine withdrawal.
Oculomucocutaneous syndrome	Stop drug Substitute any other β blocker

adrenoceptor antagonism rather than carcinogenicity by other mechanism Against the beta blocker theory of carcinogenesis is the fact that many beta blocking drugs (including many described in this series) have successfully passed stringent carcinogenicity testing in animals

How to choose a β blocker

The various β blocking compounds given in adequate dosage have comparable anti hypertensive anti arrhythmic and anti anginal effects Therefore the β blocking drug of choice in an individual patient is determined by the pharmacological and pharmacokinetic differences between the drugs in conjunction with the other medical conditions the patient might have (Table III)

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Special report

Classification of cardiac arrhythmias and conduction disturbances

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In our previous report on the definition of terms related to cardiac rhythm[1] we stressed the importance of adequate definition and classification of electrocardiographic (ECG) findings Having for the time being completed the list of definitions we accepted the assignment to proceed with the classification of arrhythmias and conduction disturbances In doing so the following points were agreed

1 Basic classification should be wide and should cover all relevant aspects of cardiac rhythm In addition it should be flexible and easily allow for modifications and extensions

2 Classification should primarily be concerned with those aspects of cardiac rhythm which can be deduced from a surface tracing As a consequence it should be mainly descriptive and with few exceptions (e g re entry entrance block concealed conduction) avoid the enumeration of mechanisms of arrhythmias and conduction disturbances

IO	DS	DR	IC	VR	SPEC
SV	REG		EX		
V	IRR		AV		
ARTP			IM		
			VA		

Fig 1 Basic classification scheme for arrhythmias and conduction disturbances. See text for explanation *IO* = impulse origin *DS* = discharge sequence *DR* = discharge rate *IC* = impulse conduction *VR* = ventricular rate *SPEC* = special phenomena *SV* = supraventricular *V* = ventricular *ARTP* = artificial pacemaker *REG* = regular *IRR* = irregular *EX* = exit *AV* = atrioventricular *IM* = intramyocardial *VA* = ventriculo-atrial.

3 Definition and classification are the hallmarks of a coding system which in turn may serve as an annotation system for ECG reading and reporting and as a key to storage and retrieval[2,4] The possibilities of coding however should not interfere with subclassification In other words the manner in which the classified data can be stored and retrieved in a handy and useful way should be considered separately and could be adapted as needed to local facilities for ECG processing[3]

4 Because of diversity of opinion and differences in technique of recording and measurement criteria for the diagnosis of various arrhythmias and conduction disturbances have not been laid down although the urgent need for this is fully recognized

At present the most detailed system of classification for arrhythmias is that of Katz and Pick[5] in which various disturbances of impulse forma

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Table I Classification according to impulse origin

1 Supraventricular
  - I Sino atrial (SA) node
  - II Atrium (excluding SA node and atrioventricular (AV) junction)
    - A. Right
    - B Left
    - C Multifocal
    - D Unspecified
  - III AV junction
  - IV Unspecified supraventricular

2 Ventricular
  - I Right
  - II Left
  - III Septal
  - IV Multifocal
  - V Unspecified

3 Impulse origin undetermined (supraventricular or ventricular)

4 Artificial pacemaker †
  - I Atrial pacing
    - A No sensing function (asynchronous fixed rate)
    - B Atrial sensing inhibited mode
    - C Atrial sensing triggered mode
  - II Ventricular pacing
    - A. No sensing function (asynchronous fixed rate)
    - B Atrial sensing triggered mode
    - C Ventricular sensing inhibited mod
    - D Ventricular sensing triggered mode
  - III Atrioventricular pacing
    - A. No sensing function (asynchronous fixed rate)
    - B Ventricular sensing inhibited mode

See also Table VI 8 and Ref 1 regarding multifocal rhythm
Classification according to the recommendations of the Tenth Bethesda Conference on Optimal Electrocardiography

tion and conduction are grouped according to well defined entities To update this system would involve the major task of summarizing all possible combinations of arrhythmias and conduction disturbances, including those recently identified Therefore this Task Force has selected the analytical approach proposed by Schamroth and Friedberg[4] This is based on the systematic analysis and classification of cardiac rhythm according to *impulse origin discharge sequence* and *impulse conduction* To these have been added *discharge rate ventricular rate* and a group of *special aspects* related to impulse formation and/or conduction (Fig 1) Each of these components can be subdivided in varying degrees of depth depending on the interest of the user Accordingly the cardiac rhythm—be it normal or abnormal—can be characterized and classified with respect to the characteristics of the compo

Table II Classification according to discharg (impulse) sequence

1 Single or up to two consecutive discharges
  - I Premature impulses (excluding manifest parasystolic impulses)
    - A. Extrasystoles
      - a Doublet (couplet)
      - b Bigeminy
      - c Trigeminy quadrigeminy etc.
      - d R on T phenomenon
      - e Other patterns
    - B Captures
    - C Unspecified
  - II Escapes

2 Regular rhythms
  - I At inherent rate (including escape rhythm)
  - II Bradycardia
  - III Accelerated rhythm
  - IV Tachycardia
  - V Flutter
    - A. Typical
    - B Atypical

3 Irregular rhythms
  - I At inherent rate (including escape rhythm)
    - A. Respiratory
    - B Non respiratory
      - a Ventriculophasic
      - b Arrest
      - c Other
  - II Bradycardia
    - A. Respiratory
    - B Non respiratory
      - a Ventriculophasic
      - b Arrest
      - c Other
  - III Accelerated rhythm
    - A Respiratory
    - B Non respiratory
      - a Ventriculophasic
      - b Arrest
      - c Other
  - IV Tachycardia
    - A. Respiratory
    - B Non respiratory
      - a Ventriculophasic
      - b Arrest
      - c Other
  - V Fibrillation

nents mentioned above Only those aspec considered relevant to a given rhythm are ind cated When the activity of two or more pac makers is evident in a single tracing each shou be specified and analyzed separately even thou their joint activity may constitute a well defin entity as in atrioventricular dissociation a some manifestations of the sick sinus syndron For instance sinoventricular dissociation due

Table III Classification according to rate of discharge

1 20 or less/min
2 21–30/min
3 31–40/min
4 41–50/min
5 51–100/min
6 101–150/min
7 151–200/min
8 201–250/min
9 More than 250/min

Table IV Classification according to impulse conduction

1 Conduction from a pacemaker (exit of an impulse)
- I Normal or presumably normal
- II First degree block
- III Second degree block
  - A Type I (Wenckebach)
  - B Type II (Mobitz II)
  - C Advanced
- IV Unspecified block (concealed discharge)
- V Impaired conduction presumably due to physiological refractoriness
  - A Delayed conduction
  - B Intermittent failure

2 Atrioventricular conduction
- I General classification
  - A Normal
  - B First degree block
  - C Second degree block
    - a Type I (Wenckebach)
    - b Type II (Mobitz II)
    - c Advanced
  - D Third degree block
  - E Unspecified block
  - F Impaired conduction presumably due to physiological refractoriness

Applicable to single premature impulses and escapes (Table II 1) See Ref 1 regarding second degree block

Only applicable to sinus rhythm and not necessarily implying conduction which is faster than normal. See also Ref 1 regarding short PR syndrome

Table IV Cont d

    - a Delayed conduction
    - b Intermittent failure
    - c. Persistent failure (duration unspecified)
  - G Short PR interval
  - H Alternation of conduction
- II Bundle branch and fascicular conduction
  - A. Normal
  - B Right bundle branch block (RBBB)
    - a Incomplete
      - (1) Intermittent (transient, non permanent)
      - (2) Persistent (duration unspecified)
    - b Complete
      - (1) Intermittent (transient non permanent)
      - (2) Persistent
  - C Left bundle branch block (LBBB)
    - a Incomplete
      - (1) Intermittent
      - (2) Persistent
    - b Complete
      - (1) Intermittent
      - (2) Persistent
  - D (Left) Anterior fascicular block (LAFB)
    - a Intermittent
    - b Persistent
  - E (Left) Posterior fascicular block (LPFB)
    - a Intermittent
    - b Persistent
  - F Combinations of bundle branch and fascicular block (specify)
  - G *Impaired conduction presumably due to physiological refractoriness* (aberrant conduction)
    - a Right
    - b Left
    - c Right and left
    - d. Unspecified

3 Intra myocardial conduction
- I Intra atrial conduction delay (including aberrant atrial conduction)
- II Intra atrial block
- III Unspecified (non specific) intraventricular conduction delay or block

4 Ventriculo atrial conduction
- (See general classification of AV conduction Table IV.2 I)

ventricular tachycardia with retrograde block is classified under the heading of *Sinus rhythm with failure of AV conduction due to physiological refractoriness in the AV junction* (possibly with the addition of ventricular capture or fusion) as well as separately under the heading of *ventricular tachycardia with retrograde block* (usually third degree) The same reasoning applies to the classification of alternating rhythms

Deviation from this rule is appropriate whenever separate analysis would imply repetition of identical statements For example with multiform ventricular activity the site of origin is classified as multifocal ventricular when it can be reasonably assumed that the alteration in QRS configuration is due to a difference in site of impulse formation in the ventricle (e g multifocal ventricular parasystole) When this is not the case it is preferable to indicate the site of origin as unspecified ventricular with an additional

Table V Classification according to ventricular rate

See classification according to rate of discharge (Table III)

Table VI Special aspects related to impulse formation and/or conduction

1 Artificial pacemaker function
  I. Normal
  II Defective
    A. Pacing
    B Sensing
    C Pacing and sensing
2 Concealed conduction
  I. In a pacemaker
  II In the AV junction
  III In the subjunctional region
  Effect of concealment (applicable to all sites mentioned above)
    A. Impairment of conduction
    B Facilitation of conduction
    C Resetting of subsequent discharge
    D Combinations
3 Coupling interval
  I Constant (80 msec or less)
  II Variable
4 Entrance block (protection)
  I. Parasystole
    A. Intermittent
    B Persistent
  II. Other
5 Enhancing mechanisms
  I. Supernormality
    A. Of conduction
    B Of excitability
  II Other
6 Gap phenomena
  I. In the AV conduction system
    A. During anterograde conduction
    B During retrograde conduction
  II In other parts of the heart
7 Isorhythmic dissociation
8 Multiform configuration of wave forms
  I Bidirectional (alternating)
  II Fusions
    A Atrial
    B Ventricular
  III Torsade de pointes
  IV Unspecified
9 Pre-excitation
  I Atrial
    A. Intermittent
    B Persistent
  II Ventricular
    A. WPW pattern
      a. Intermittent
      b Persistent
    B Short PR syndrome
      a. Intermittent
      b Persistent
10 Re-entry
  I Atrial
  II AV junctional
  III Ventricular
  IV Combined atrial and ventricular
  Further specifications, applicable to above
    A. Concealed
      a. Single
      b Repetitive
    B Manifest
      a. Single
      b Repetitive

A specific type of irregular and usually repetitive ventricular tachycardia in which specific etiological factors are involved and in which, during each paroxysm, the QRS axis progressively changes, so that in some leads the ventricular complex appears to twist around the isoelectric line

statement indicating multiform configuration of the wave forms (see Table VI 8)

Descriptive statements such as uniform and multiform do not fit into a classification according to impulse origin (Table I) discharge sequence (Table II) and impulse conduction (Table IV) This is especially true in those cases where one is uncertain as to the mechanism underlying the alteration in configuration—e g bidirectional tachycardia and some cases of multiform ventricular or atrial extrasystoles

While such an approach may at first look strange it does in fact follow a logical order and allows for easy extension of the subdivision of individual components For example the elect[rо]physiologist may wish to analyze AV conducti[on] with regard to conduction in the AV junction a[nd] the subjunctional region or he may even wish [to] distinguish between conduction in the approa[ch] fibers the AV node and the common AV bund[le] Also some electrocardiographers may wish [to] distinguish between typical and atypical typ[es of] AV block, or between type I type II a[nd] advanced intermittent bundle branch blo[ck] Likewise some may wish to classify defecti[ve] artificial pacemaker function in terms of tra[n]sient or persistent failure

The following Classification Tables constitu[te] a basic framework and are considered se[lf] evident For nomenclature the reader is referr[ed] to the report on definitions[1] Disagreement ma[y] arise over the use of the adjectives *intermitte[nt]*

and *persistent* In the present context dealing with the classification of single electrocardio grams intermittent refers to an electrocardio graphic phenomenon during a particular rhythm which lasts less than the duration of the available record If it continues throughout the recording it is classified as persistent From a clinical point of view however such manifestations may well be of temporary nature For that reason *persis tent* referring to an established but not necessari ly an ever present phenomenon is preferred to *permanent* Intermittency which manifests as persistent in a given ECG will be apparent from different statements in consecutive records e g persistent bundle branch block in one record and normal conduction in another

The members of this Task Force are indebted to Mrs. G van Eck for secretarial assistance in the preparation of the manu script

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Annotation on hyponatremia

A low plasma sodium concentration happens in many clinical conditions. In some such as severe heart failure adrenal failure renal failure or severe saline depletion it has little diagnostic usefulness except as confirmation of the severity of the condition and its contribution to the clinical state is not clear In other conditions such as carcinoma of the lung chest infection or central nervous system disorders hyponatremia may be found by chance although it may be suspected because of headache confusion or drowsiness

The causes of hyponatremia have usually been classified on the basis of largely assumed defects in the osmoreceptor—ADH—kidney system This system controls the plasma osmolality and plasma sodium concentration through regulation of water intake and urine flow However ADH secretion is increased in "volume depletion" and water is retained even at the price of a low plasma sodium concentration and low plasma osmolality A fall in the plasma sodium concentration (osmolality) is therefore due either to a defect in the osmoreceptor—ADH—kidney system or a response of the system to non-osmotic stimuli, or to the uncontrolled production of ADH outside the system (ectopic production)

Bartter and Schwartz defined a discrete pathophysiological entity which they called "syndrome of inappropriate secretion of ADH (SIADH) They used the term inappropriate to indicate continued secretion of ADH (for which they had only indirect evidence) in the presence of a low plasma osmolality But what is an inappropriate secretion in relation to the plasma osmolality may be appropriate in relation to other physiologic stimuli to ADH secretion such as plasma volume depletion For this reason it has been argued that the important decision is whether the ADH is secreted from the pituitary or an ectopic site The latter will give autonomous secretion However this distinction probably cannot be made on the basis of plasma ADH concentration and would require either localization of the site of secretion or a test for feedback control of secretion

These difficulties led us to suggest a simple descriptive terminology such as hyponatremia with heart failure hyponatremia with chest infection hyponatremia with carcinoma of the lung and so on

Two questions can be posed which patients should be treated specifically for the hyponatremia and what is the treatment of choice? When hyponatremia occurs with heart failure adrenal failure renal failure or saline depletion it is the underlying condition rather than the hyponatremia which is usually treated In the absence of these conditions there is a tendency to assume the condition is SIADH due to carcinoma of the lung and that specific treatment of the hyponatremia is required. However in a recent study of 1[illegible] patients with severe hyponatremia we found that chest infection was as common as carcinoma of the lung when the organ failures and saline depletion had been excluded. Treatment of the chest infection corrected the hyponatremia in a few days and specific treatment of the hyponstremia was not necessary This is oppo- to the view held by Schrier

The decision to correct the hyponatremia directly should be based on the presence and severity of symptoms and not on the plasma sodium concentration There is poor correla- between the plasma sodium concentration and the sever- of symptoms probably because a recent rapid fall in osmolality has more clinical effect than a new abnormal steady state, where compensatory changes may have happened to lessen the cellular changes.

The two approaches to treatment are to deprive the patie- of water or to diminish the renal responsiveness to ADH Th- initial aim of water deprivation is to produce a negative wa- balance but the maximum rise in plasma sodium which can b- expected is about 4 mmol. in 3 days. The rate of removal o- water can be increased by giving furosemide with sodium replacement The long term aim of water deprivation is t- precisely match water intake to water losses, but it is difficu- to imagine that this can be precisely achieved by jug- the water intake All things considered it seems very doubtf- that water deprivation is an effective or feasible treatment fo- chronic hyponatremia, even from excess ADH due to carcin- ma of the lung and its effects are too slow to be of much use the acute situation

The alternative approach to treatment is to diminish t- renal responsiveness to ADH Lithium was not effective b- demeclocycline was although it may impair renal functio- With demeclocycline the plasma sodium increased to norm- and remained so in spite of a free and therefore variable wa- intake In other words feedback was restored to the syste- The reason was probably that the effect of ADH on the ren- tubules was almost completely blocked (maximum ur- osmolality only 250 mmoles/kg) so that urine volume w- increased and water balance was achieved and maintai- through the control of water intake by the thirst mechanis- The success of the treatment therefore requires an int- thirst mechanism and access to water The advantages of t- approach over the crude approach of water deprivation - clear However we suggest that the need for any treatment chronic hyponatremia has not been established Schr- concluded that in acutely symptomatic patients, where t- response to simple water restriction may be too slow to useful demeclocycline is the treatment of choice

Hyponatremia happens in severe congestive heart failu- but treatment is usually aimed at the heart failure Howe- treatment of the hyponatremia with demeclocycline - recently been tried, presumably on the assumption that hyponatremia was due to excessive secretion of ADH Ot- possible causes of the hyponatremia where demeclocycl- would presumably not be effective would be resetting of osmoreceptors at a lower level or decreased glomerular filt- tion rate or increased proximal tubular reabsorption of sod- and water We need to decide in which patients with he-

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failure the hyponatremia is causing ill effects what is the mechanism of hyponatremia and thus what is the most effective treatment of it

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Surgical treatment of ruptured intracranial aneurysms

Although 55 years have elapsed since the condition was first recognised in life and 45 years have gone by since the first intracranial operation the treatment of subarachnoid hemorrhage from ruptured intracranial aneurysms is still controversial Even now the natural history against which the results of treatment must be measured is sparsely documented and there is only one published community study which includes death before admission to hospital

In general the condition is commonest in the middle years of life and in younger men and older women Forty per cent of patients die from the effect of the first hemorrhage most without reaching specialist neurological or neurosurgical care At least one third of the survivors die mainly from the effect of recurrent hemorrhage within the first six weeks the *mortality rate for a second hemorrhage being up to 64 per cent* and for a third 86 per cent. Thereafter there is a mortality rate in survivors of about 5 per cent annually

These depressing figures come from series of patients treated conservatively with 6 weeks bed rest and control of blood pressure The question is whether surgery can do any better The early published results were not encouraging and no convincing difference from controls emerged in series treated by intracranial surgery to the aneurysm Only common carotid artery ligation in the neck could be shown to influence the outcome and then only in aneurysms of the internal carotid artery This procedure has the advantage of being simple to perform but carries a risk of hemiplegia and sometimes death and usually lea es the aneurysm still filling with a risk of later hemorrhage Recent work has indicated ways of reducing these risks, and the procedure is likely to retain a place in treatment especially when an aneurysm appears unsuitable for direct intracranial attack.

Intracranial surgery to the aneurysm has the aim of excluding the aneurysm from the circulation by occluding the neck with a ligature or more usually a metallic clip This can only prevent further bleeding and unless an intracerebral clot can be removed cannot be expected to restore neurological function The operation must leave the cerebral vessels patent or major neurological deficit will result and where clipping the neck of the aneurysm might occlude vessels investment of the aneurysm to reinforce the wall is an acceptable alternative treatment Successful clipping or complete investment of an aneurysm should leave the patient permanently protected *from further hemorrhage from that aneurysm*

Most neurosurgeons involved in this surgery are convinced that modern methods have radically altered the results of intracranial operation but it is not easy to show the contribution of this to over all management Surgery does little to save the 40 per cent of patients who die from the first recognized hemorrhage Only occasionally can a patient with a large intracerebral hematoma be rescued by immediate operation and the selection of patients and the timing of operation is crucial. That patients in poor neurological state do badly with operation has been known for 20 years and several methods of grading patients as a guide to outcome have evolved It is also known that the earlier the operation in relation to the last hemorrhage the greater the chance of postoperative death or disability but that the longer the operation is

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delayed the greater the chance of death from recurrent bleeding These factors make evaluation of the place of operation and the comparison of results difficult However there is no doubt that in the hands of individual surgeons there have been striking improvements in recently reported results with mortality rates of less than 5 per cent[20] These figures have been obtained by microsurgical techniques and by improved anesthesia with hyperventilation and hypotension Hypothermia has been replaced by high dose steroids for the control of cerebral edema and the protection of the brain Barring technical problems, a nil mortality and morbidity now appears to be within reach for patients in grades 1 and 2 operated on 10 days after the last hemorrhage And yet the contribution of this to over all management is not clear since these patients in better grades are those least at risk of recurrent hemorrhage Earlier surgery perhaps to all patients on the day of admission while possibly producing more survivors, would result in a morbidity and mortality rate which few neurosurgeons could accept In practice delay in operating allows some natural selection to occur since most patients who have been severely damaged by the initial hemorrhage will die whatever is done and many of the others will improve within a few days to become better operative risks

The work of Alvord and co workers on predicting the natural outcome in any patient in relation to clinical grade and interval since the last hemorrhage is important in providing standards against which the results of any treatment can be judged Set against these figures many surgical results give little ground for complacency However there are areas where over all results might be improved

First all small warning hemorrhages must be diagnosed and patients referred for angiography while in a good clinical state Such warnings often precede a major hemorrhage and may be missed or ignored with serious consequences when further bleeding occurs[8] The diagnosis is not always easy and lumbar puncture should always be performed if subarachnoid hemorrhage is suspected Second some way must be found of preventing or treating the cerebral ischemia which is associated with vasospasm after subarachnoid hemorrhage and is a common cause of death or disability The onset is usually within a few days of the hemorrhage and is followed by progressive neurological deterioration Operation does not prevent this and may on occasions appear to precipitate it when surgery is undertaken in the first 10 days after the hemorrhage The mechanism of this vasospasm is poorly understood and no therapy to influence it has yet been found Third patients must be protected from recurrent hemorrhage while awaiting the optimum time for operation There is evidence to suggest that antifibrinolytic agents may contribute to this by preventing or delaying dissolution of clot around the aneurysm These problems look to be within reach of solution but even then the management of patients with ruptured intracranial aneurysms will continue to demand from neurosurgeons not only high operative skills but also great clinical judgment if optimum results are to be obtained

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Treatment of orthostatic hypotension with indomethacin

Orthostatic hypotension may occur as a result of volume depletion or autonomic failure The conditions associated with volume depletion such as hemorrhage gastrointestinal fluid loss and Addison s disease usually respond to fluid repletion and mineralocorticoid therapy Autonomic failure may be responsible for postural hypotension in idiopathic orthostatic hypotension Shy Drager syndrome and in certain patients with idiopathic parkinsonism In the past suggested therapy included plasma volume expansion by salt and mineralocorticoids reduction of pooling in the legs by elastic stockings or use of pressor drugs with or without monoamine oxidase inhibitors Despite these measures orthostatic hypotension secondary to autonomic failure is difficult to treat

We studied four such patients with a clinical diagnosis of Shy Drager syndrome who had reductions in blood pressure of 20 mm Hg or more upon standing in association with orthostatic symptoms of dizziness and fainting in addition to their neurological abnormality Plasma renin activity was low in each patient and did not rise appropriately with salt restriction and diuretic stimulation Aldosterone levels were normal and rose with diuretic therapy Plasma volume plasma dopamine β hydroxylase urinary catecholamines metanephrines and vanillylmandelic acid (VMA) were normal. The combination of a vasopressor (ephedrine) and a β blocker (propranolol) was not beneficial Two of the four patients responded to fludrocortisone with significant increase in systolic and diastolic blood pressure and with symptomatic relief of hypotension However all of the four gained 1 to 2 kilograms in weight and developed dyspnea or frank congestive heart failure On the other hand the administration of indomethacin (75 to 150 mg /day) increased both systolic and diastolic blood pressure in all patients relieved orthostatic symptoms and enabled the patients to walk again When indomethacin was discontinued in one patient after nine months of successful therapy the blood pressure fell to pretreatment levels within 48 hours. When indomethacin was reinstituted the blood pressure rose again within 24 hours.

Indomethacin inhibits prostaglandin synthesis and several prostaglandins are potent vasodilators Our experience raises the possibility that a relative or absolute excess of vasodilator prostaglandins may play a role in some patients with orthostatic hypotension Recently we have found that aspirin and other inhibitors of prostaglandin synthesis can be beneficial albeit less than indomethacin in alleviating hypotension in two patients with orthostatic hypotension It remains to be seen whether the salutary response to indomethacin reflects altered interrelationship between the autonomic nervous system and prostaglandins or some other mechanism

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Of solo practice

The rendering of excellent and unselfish service to sick people is the responsibility of all physicians Patients always expect the best service from their doctors The doctor who is in practice alone or with only one or two other doctors has the opportunity of rendering the best service to his patients He is free to practice as he wishes He collects the clinical data himself He can consult with the best consultants in the world regardless of where they are He is not restricted to a closed group of physicians He exposes himself openly to all of his associates in medicine and is viewed without prejudice or conflicts of interest The quality of his service is reviewed by hospital services such as pathology microbiology practice

review committees etc., and not only by members of his own restricted group His practice is constantly monitored by others in competition with him and his performance becomes well known to his fellow physicians.

But above all, he is in a position to provide the best service to his patients free from restrictions by other physicians of a large group His association with the patient is intimate and he retains full responsibility at all times for his patient The patient always knows who his doctor is and for whom to call when in need. The progress of treatment and the patient s health and his entire family are known to his "solo doctor" The patient sees the same doctor all the time Thus the patient s problems are always known to his private physician since he is the only physician to attend the patient at times.

Solo practice provides the greatest emotional satisfactio the patient and the doctor and even though a solo practi extremely demanding it is extremely rewarding Solo pr practice is fun when the doctor is a master clinician, ho highly motivated and dedicated This is true for all sub cialties of medicine and surgery as well

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Importance of correct diagnosis in cardiac conditions

To the Editor

Dr Todd deals in his paper with two of the most frequent cardiomyopathies ischemic and idiopathic The author feels that since patients with ischemic and idiopathic cardiomyopathies are given diuretics digitalis and diet a correct diagnosis established by coronary angiography is unnecessary

This approach to a basic problem of diagnosis and management represents an oversimplification

Pathological processes that injure or obstruct small arteries of the heart are commonplace in diabetes mellitus Such changes have been described in diabetic patients with enlarged hearts and normal extramural coronary arteries Diabetic patients with intractable angina caused by involvement of the large coronary arteries may benefit from surgical treatment Diabetic patients with angina and normal extramural coronary arteries benefit from medical treatment. The correct diagnosis in both groups is made by coronary arteriography Myocardial dysfunction (cardiomyopathy) without coronary artery disease has been recently reported in diabetic subjects of juvenile onset and azotemic nephropathy These patients were evaluated with coronary angiography before renal transplantation

Patients with disease of the myocardium often tolerate congestive failure for longer periods of time than do patients with myocardial involvement due to coronary artery disease hypertension or valvular disease However we observed that in three of four patients with severe coronary artery disease masquerading cardiomyopathy proper medical management including diet and bed rest may play a certain role in prolonging the patients life span

The most obvious change in congestive cardiomyopathies is cardiac dilatation which is best seen in the left ventricle but may involve other chambers There may be murmurs of mitral and tricuspid regurgitation A late stage of diffuse coronary artery disease or valvular disease may show identical changes In such situations invasive studies including ventriculography are indicated

In Duchenne s muscular dystrophy a recent report describes predominant cardiomyopathy The cardiac manifestations may antedate recognition of neuromuscular disease The electrocardiogram mimics myocardial infarction There is no correlation between the degree of skeletal muscle disease and the severity of cardiac symptoms or electrocardiographic changes The coronary arteries are normal James attributed the clinical and electrocardiographic abnormalities to degenerative changes

Patients with enlarged hearts due to ischemic cardiomyopathy and congestive heart failure may present myocardial aneurysms The correct diagnosis made by invasive procedures, saphenous bypass and aneurysmectomy result in prolongation of life

We agree with Dr Todd that coronary arteriography is risky and expensive It should be performed in well selected cases only A correct diagnosis and proper treatment often requires the judicious use of coronary arteriography

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Further thoughts on the diving reflex

To the Editor

The paper by Drs Hamilton Moodie and Levy in the March issue of the JOURNAL indicates the diving reflex can be used successfully to terminate supraventricular tachycardia in a neonate The authors state they manually occluded the infant s nostrils to prevent aspiration when her face was placed in ice water

review committees etc and not only by members of his own restricted group His practice is constantly monitored by others in competition with him and his performance becomes well known to his fellow physicians

But above all he is in a position to provide the best service to his patients free from restrictions by other physicians of a large group His association with the patient is intimate and he retains full responsibility at all times for his patient The patient always knows who his doctor is and for whom to call when in need. The progress of treatment and the patient s health and his entire family are known to his "solo doctor" The patient sees the same doctor all the time Thus the patient s problems are always known to his private physician since he is the only physician to attend the patient at all times

Solo practice provides the greatest emotional satisfaction to the patient and the doctor and even though a solo practice is extremely demanding it is extremely rewarding Solo private practice is fun when the doctor is a master clinician, honest, highly motivated and dedicated This is true for all subspecialties of medicine and surgery as well.

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Book reviews

Biochemical Aspects of Prostagland ns and Thromboxanes Edited bv Norman Kharasch and Joseph Fried New York 1977 Academic Press Inc 245 pages.

These proceedings of a symposium held in Santa Monica California in December 19 6 are concerned with important new developments and interests in medicine The prostaglandins and thrombaxanes have interested many physiologists and physicians recently This publication provides important biochemical information on the subject The participants in the symposium were numerous and the papers presented are interesting and limited to selected aspects of the biochemistry of these interesting substances. It is beyond the scope of this review to discuss each paper except to indicate that the selected aspects of the vast problems related to prostaglandins are well presented Physiologists and physicians who use these agents will find the book to be useful even though somewhat brief and complex This is a useful book for all individuals interested in prostaglandins

Atherosclerosis IV Edited by G Schettler Y Goto Y Hata and G Klose Berlin Heidelberg and New York, 1977 Springer Verlag 897 pages Price $49 70

This lengthy book contains the proceedings of the Fourth International Symposium on Arteriosclerosis held in Tokyo during August 1976 The contributors to the symposium and the participants were from 36 countries O hima presented data indicating a decided decline in the incidence of cardiac death for Japanese for all ages from 40 to 65 whereas at the same time the total number of deaths is increasing The source of the data is not indicated He attributes the increase in life span to better health care Raw" data are in fact not shown throughout the book an important aspect of present day writing

This large book is divided into six parts each part including many papers The symposium was concerned with the arterial wall lipoproteins regression of arteriosclerosis epidemiology pediatric aspects of atherosclerosis and treatment of human arteriosclerosis The book really contains little that is new and certainly no great discovery related to this plague is indicated The book is a good reference source and should be included in the library of those who are studying arteriosclerosis and those who are interested in the disease The book is well bound and the bibliography extensive This publication is valuable but expensive

The First 24 Hours in Myocardial Infarction Edited by F Kaindl O Pachinger and P Probst New York 1977 Verlag Gerhard Witzstrock 219 pages

This publication summarizes the discussions at an international symposium held in Vienna during June 1977 The book contains nothing new Like all symposia the material presented has been almost entirely previously published The value of such a book is limited to those who do not follow the medical literature closely The presentations are so brief and so numerous that each paper represents a superficial review of the subject For example the discussion of vasodilators is presented in two pages new apsects of cardiogenic shock in three pages, red cell mass and plasma volume in three pages etc It would have been more effective if a few selected aspects of the problem of myocardial infarction during the first 24 hours were discussed more extensively and very critically

Books received

Essentials of Pediatric Cardiology By James H Moller M D Philadelphia 1978 F A Davis Company 202 pages Price $35 00

Achalasia of the Cardia By H R S Harley M D., F R C S Bristol 1978 John Wright & Sons Ltd 174 pages

Medicine and the Reign of Technology By Stanley Joel Reiser New York, 1978 Cambridge University Press 317 pages Price $14.95

Announcements

First Pan American Congress on Critical Care Medicine

The first Pan American Congress on Critical Care Medicine will be held in Mexico City on September 23 through 27 1979 at the María Isabel-Sheraton Hotel Paralleling the congress will be an International Meeting of Nurses Specializing in Intensive Care Official languages of the congress will be Spanish and English with simultaneous interpretation Subjects covered will include recent advances and major problems in the management of the critically ill embracing shock sepsis nephrology nutrition and metabolism cardiology cerebral function and pulmonary disease Other aspects including legal, ethical and financial as well as an examination of teaching and certification will be discussed. There will be free papers and poster presentations For further information, contact 1st Pan American Congress on Critical Care Medicine Avenida Veracruz 93-203 Mexico 11 D F Mexico Telephone 553-13-11

Nineteenth Workshop in ECG

The nineteenth Workshop in Electrocardiography for Nurses and Physicians will be held on October 4 through 11 1979 at the Sheraton Sand Key Hotel Clearwater Beach, Fla The workshop is sponsored by the Rogers Heart Foundation For further information contact Anne S Criss, Executive Coordinator Rogers Heart Foundation St Anthony s Hospital, St Petersburg Fla 33705 Telephone (813) 894-0790

International Symposium on Animal and Human Influenza

An International Symposium on Animal and Human Influenza will be held in Maisons-Alfort France on September 13 and 14 1979 at the *Ecole Nationale Vétérinaire d Alfort* Subjects covered will include an influenza virus review a discussion of viral epidemiology and ecology the inter relationship between animal and human influenza and an examination of influenza vaccines and chemotherapy For further information contact Secretariat of the Department of Microbiology-Immunology (Prof Ch Pilet) Ecole Nationale Vétérinaire d Alfort 7 avenue du Général de Gaulle, 94704 Maisons Alfort France

Dr Frank N Cochems Competition

The University of Colorado School of Medicine announces the Fifteenth Annual Cochems Competition A prize of $250 will be awarded to the author of the best paper concerning "Thrombophlebitis and Basic Vascular Problems. It should be concerned with the mechanisms or processes of vascular disease particularly thrombosis but not restricted to it. Eligibility is limited to physicians subject to U.S income tax regulations Entries must be received in triplicate on or before November 30 1979 Inquiries regarding the competition and all manuscripts should be submitted to the Dean School of Medicine University of Colorado Medical Center 4200 East Ninth Avenue #C 290 Denver Colo 80262

American Heart Journal

September 1979 Volume 98 Number 3

Editorial

Is hyperthermia a human teratogen?

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The relatively stable and high body temperature of mammals is of considerable advantage for their survival compared with poikilothermic animals It would be logical to expect an evolutionary trend toward even higher body temperatures unless this was prevented by one or a number of physiological or biochemical barriers Cowles[1] suggested that the effects of heat on spermatogenic cells was one such barrier Certain phases of spermatogenesis are extremely sensitive to elevated temperatures but the elaborate heat exchange system in scrotal mammals effectively protects the proliferating male gamete precursors from all but extremes of elevation Spermatogenic cells however are not unique in their sensitivity to elevated temperatures Proliferation of cells in cultures derived from normal or malignant tissues is also disrupted by heat[2, 3] and induced hyperthermia has been used in the treatment of human malignant growths [5] In all these systems the rate of cellular proliferation is high so it appears that rapidly dividing cells are much more sensitive to heat than non-dividing cells

Cellular proliferation is also extremely rapid in embryonic tissues and it is not surprising that heat has been found experimentally to produce congenital abnormalities in a number of avian and mammalian species Some of the early experiments with incubating chickens were reported nearly 50 years ago[6] and particularly over the past 20 years an increasing number of mammalian species has been reported to be sensitive to malformation if heat is applied during early gestation It was widely recognized before this time that excess heat during pregnancy resulted in increased prenatal mortality with resorption and reduction in the birthweight of affected newborn[7]

Experimental induction of hyperthermia in pregnant mothers has resulted in a wide variety of malformations including hernias[8] tooth defects[9] talipes[10] vertebral abnormalities[11] micrencephaly[12, 13] cataracts[8] microphthalmia[14] arthrogryposis[1] and anencephaly [16] Abortions commonly followed exposure and stillbirth and post natal death rates were high among affected newborn Rats[17] and mice were used in initial experiments but more recently heat has been shown to affect prenatal development in guinea pigs[8] rabbits[8] hamsters[16] sheep and primates[20, 21]

Despite the extensive literature which has accumulated on the effects of hyperthermia on pregnancy and prenatal development in laboratory and domestic animals and in primates evaluation of its effects in human pregnancy has only just begun Dr David Smith of the University of Washington with his co workers has published the results of two retrospective surveys [23] which indicated that hyperthermia induced in pregnant women by a variety of viral or bacterial infections or possibly by sauna bathing was associated with the birth of children with a number of

From the Department of Veterinary Clini al Stud es Uni ers ty of Sydney

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Reprint req ests Dr Marshall J Edw rd Un rsity of S dn y Dept of Veterinary Clinical Stud es N S W 2006 Sydn y Australia

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Epidemiological studies and reports based on birth registers have shown a frequent association between maternal influenza[25, 29] or maternal fever and the birth of children with malformations especially of the central nervous system Most animal studies indicate that the brain is the major and often the only target organ and if hyperthermia does prove to be a human teratogen micrencephaly could be expected to be a common finding

If this is the case what is the significance of retardation of brain growth in the absence of other obvious abnormalities? The deficit in brain size in experimental animals has varied from minor to severe and depended in its extent on the timing of maternal hyperthermia its elevation above resting levels and its duration Where the deficit was significant the learning ability was impaired and the continuum of size deficits from severe to minor appeared to be associated with corresponding learning deficits In effect although a number of animals with minimal deficits in brain size and function might still be within the normal ranges for these attributes they might have not achieved their genetic potential It would be extraordinary for an organ permanently retarded in its growth to be as efficient in its function as a normal organ

This concept is supported by the studies on children who were exposed *in utero* to radiation from the Hiroshima atomic bomb Exposure during the third to fifteenth week to estimated doses of 50 rads or more was associated with an increased incidence of microcephaly growth retardation and mental retardation[30] which were frequently the only abnormalities to be found Using the developing brain of guinea pigs as an assay system it has been found that 1° C elevation of maternal temperature above the threshold has a similar effect as about 50 rads of gamma radiation if given during the most susceptible stage of gestation

In many respects the effects of hyperthermia closely resemble those of radiation Both agents kill proliferating cells radiation affecting cells in the post mitotic phase of the generation cycle and hyperthermia affecting cells which are at about the stage of mitosis Most defects produced by them are attributed initially to cell death but the loss of certain cells might be critical in determining the further development of an organ For example if heat is applied to the guinea pig embryo during early neuroblast proliferation it destroys neuroblasts and the consequent deficit of neurones apparently cannot be made up by additional divisions In some way the number of neurones remaining determines the extent of glial cell proliferation as the eventual number of glial cells is also proportionately reduced. The fewer oligodendroglia produce less (but appropriate) amounts of myelin The net result is a brain which is normal in shape containing the correct concentrations of neurones glial cells and myelin but which is irreparably deficient in size and function[31]

In assessing the risk of hyperthermia in human pregnancy the timing of exposure its duration and its elevation would be of major importance There is likely to be considerable variation in the susceptibility between individuals as is found with nearly all teratogens In experimental studies, even littermates which presumably would have been exposed to similar maternal temperature elevations frequently show markedly different susceptibilities to its effects Within an individual embryo different organs and tissues have differing susceptibilities but in all species the brain has been the main target organ presumably because of its intense proliferative activity during susceptible stages The effects on brain growth might be subtle and in the human they could be difficult to measure and might only be manifested as lowered intelligence or behavioral disturbances as is found in primates[2] Perhaps the most conveniently measured index of brain size would be skull circumference It is known that in its lower ranges skull circumference is related to mental retardation[32]

Heat is a naturally occurring and relatively uncontrolled environmental agent It is essential to life but in excessive amounts is teratogenic to some animals through its toxic effect on cell division Its possible contribution to human congenital malformations should be explored carefully including its effects on brain growth as there is so much which could be lost

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Clinical communications

Predicting results of coronary angiography

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Numerous studies have demonstrated that clinical epidemiological and psychosocial factors act to increase the risk for clinically significant cardiac disease This study examines the ability of four risk factor orientations to predict not the *clinical* manifestations of coronary disease but the presence of *anatomical* narrowing of the coronary arteries as demonstrated by angiography These orientations are clinical epidemiological psychosomatic and combined Each orientation utilizes a different data base regarding patient assessment

For the purpose of this study the clinical orientation uses only such data that are readily obtainable from a brief examination of the patient The epidemiological orientation takes cognizance of the patient s past exposure to presumably deleterious substances or experiences This orientation utilizes slightly newer and sometimes more complicated laboratory studies and more detailed information about the patient s past history The psychosomatic orientation relies on in depth interviews and psychometric tests in an effort to explore possible psychosocial antecedents for coronary artery disease Finally the combined orientation adds the above three perspectives into one overarching prediction of the phenomenon

The literature is quite substantial on each of the respective viewpoints Unfortunately few studies compare the *relative predictive success* of the different schools of thought instead most studies confirm or deny the adequacy of only one theoretical viewpoint

Methods

Our sample was derived from patients awaiting cardiac catheterization at Massachusetts General Hospital Patients came to cardiac catheterization with a presumptive diagnosis of coronary artery disease as evidenced by chest pain or past myocardial infarction Patients with the following criteria were included in the study men whose ages ranged between 18 and 70 years who had consent of their primary physician who were of average intelligence English speaking and who indicated willingness to participate in follow up studies Patients were excluded from study if they were in critical medical condition (e g cardiogenic shock) if they had some other major illness (e g malignancy) or if they had some other manifestation of heart disease such as valvular heart disease or cardiomyopathy All such exclusions were made prior to any risk factor assessment

Contact was attempted on 108 patients Three patients physicians refused participation three patients refused participation three patients

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Table I Risk factor orientations

Clinical	Epidemiological	Psycho somatic
History of myocar dial infarction	Age	Anxiety
Extent of angina	Fasting cholesterol	Depression
Any ECG abnor malities	Fasting triglyceride	Anger
ECG Q waves	Blood pressure	Fatigue
Peel score	Diabetes history	Life stress
	Smoking history	Denial
	Family history	Type A

were found ineligible The final sample consisted of 99 patients better than 90 per cent of the patients in the population approached The aver age age was 49 years with a standard deviation of 9 years

Patients were seen prior to coronary angiogra phy by a research assistant who interviewed the patient administered various questionnaires and did a complete chart review

We studied a number of possible risk factors for coronary artery disease For this analysis we studied five to seven of the most salient factors per theoretical orientation (Table I) Inclusion of a greater number of risk factors is unwarranted for a study with this sample size

In those instances such as smoking history where there were two possible measurements we utilized only the one that was more strongly correlated with the extent of coronary artery disease in this sample Theoretically one should use a prespecified measure The procedure described here would tend to bias the results slightly toward significance Nevertheless we opted for this practice since we wanted each theoretical orientation to be as strong as possible before comparing their relative success

In our clinical measurements we included the following (1) history of past myocardial infarction (yes = 1 no = 0) (2) extent of angina as based on the New York Heart Association functional angina scale (scores 1 to 4) (3) any ECG abnormalities (yes = 1 no = 0) (4) presence of Q waves on ECG (yes = 2 no = 1) and finally (5) a coronary prognostic index the Peel Score at time of hospitalization

The epidemiological measurements tap the areas of age family history lipids and hyper tension diabetes and smoking history Family history was counted as positive (1 point) if a parent or sibling had onset of heart disease before age 60 or negative (0 points)

A fasting cholesterol and triglyceride were obtained in most cases a day or two prior to catheterization Rather than classify values as normal or abnormal the exact levels in milli grams per cent were used as two continuous variables in the analysis In the vast majority of cases the catheterization was an elective proce dure scheduled at a time remote from myocardial infarction

A history of hypertension was scored as defi nitely present (2 points) if there was a history of treatment probably present (1 point) if the patient had been told by a physician that he had hypertension or absent (0 points) The blood pressure on admission was taken as a measure of current hypertensive status Rather than class the systolic and diastolic pressures as normal or abnormal the values were retained and entered as continuous variables Current systolic blood pressure was the measure of hypertension most closely correlated with vessel disease in our sample and was used as our variable for hyperten sion

Diabetes was scored as definitely present (2 points) if the patient had been treated with an anti diabetic agent possibly present (1 point) if he had a history of an abnormal glucose toleran test or had been informed by a physician that he needed to be on an anti diabetic diet or absent (0 points)

Smoking history was obtained in pack years and also in current number of cigarettes smoked per day Pack years was the better predictor of coronary artery disease in our sample and was used as our measure of smoking

Our psychosomatic measurements assess the patient s current anxiety depression anger fatigue extent of recent stressful life experience denial and Type A behavior

The Profile of Mood States (POMS)[3] is an objective self administered checklist that mea sures current levels of tension depression anger and fatigue as continuous variables Rather than being self administered use of the POMS was modified by reading each adjective on the check list aloud to the patient and having him indicate his response verbally Because the responses on the depression and fatigue indices did not appro

imate a normal distribution the scores were recorded as being in the lower middle or upper third of the sample distribution

Stressful life experiences in the past four months were quantified in life change units obtained from use of a 42 item Schedule of Recent Events (SRE) The SRE measures life events varying in severity from death of a spouse to receipt of a traffic ticket[3]

Type A personality was measured with an objective questionnaire the Jenkins Activity Survey (JAS) Form B

Denial is a defensive strategy widely used by cardiac patients[5] It can be assessed with the Hackett Cassem denial interview a semi structured interview requiring about 15 minutes to administer[6] The interview measures the patient s acknowledgement of his illness his anxieties about hospitalization and his fears about possible undesirable changes in life style

A cardiologist unassociated with this study performed the angiography using the Sone s or Judkin s techniques Vessels were classified as significantly diseased if angiography demonstrated a 50 per cent or greater narrowing of the vessels diameter (equivalent to 75 per cent cross sectional area narrowing of the vessel)

A series of direct method discriminant analyses [8] tested each of the four theoretical orientations in their ability to predict which of the 99 patients would have coronary artery disease in at least one vessel Our analyses were run on an IBM 370 computer utilizing the Statistical Package for the Social Sciences[9]

For the non statistician this complex statistical approach requires further description The discriminant analysis examines many variables singly and in combination and attempts to derive an equation which will classify individuals as possessing or lacking a certain characteristic in this case vessel disease After minimizing redundancy of information discriminant analyses derive weights (coefficients) for a series of variables which maximize the separation between two groups The weighting process for the coefficients also controls for scores of variables differing in order of magnitude (e g 200 for cholesterol level *vs* 4 for angina severity) These weights are entered into a polynomial equation of form

discriminant score = ax + bx + constant

to yield a discriminant score An optimal cut point is established which allows the best separation of discriminant scores into two groups in this case vessel disease or no vessel disease Significance levels may be obtained from the canonical correlation which examines the possibility that the equation divides the population accurately merely by chance

Table II Performance of discriminant analyses derived according to different theories of risk

Theory	*Canonical correlation*	*Probability*
Clinical	0 56	< 0001
Epidemiological	0.39	<0 03
Psychosomatic	0.28	<0 39
Combined	0 65	<0 0001
Clinical and epidemiological	0 63	<0 0001

Results

Table II presents the summary success of each discriminant analysis* The clinical and combined analyses are highly successful in predicting vessel disease The epidemiologic orientation lags behind them in significance but still predicts rather well The psychosomatic orientation did not provide predictions much better than would have been expected by chance

Although the combined orientation is highly successful it entails a complex equation with 19 variables derived from three theoretical orientations We examined the three equations obtained from combining the orientations two at a time The epidemiology-clinical combination was superior to the epidemiology-psychosomatic and the psychosomatic-clinical orientation Its discriminating ability is intermediate between the clinical and the combined approach.

So far we have examined the over all accuracy of each orientation It is conceivable that some orientations may succeed at recognizing the cases but fail at recognizing the normals or vice versa To examine this question one needs to examine the dicriminant analyses as far as sensitivity (the ability to recognize true cases with a minimum of false negatives) and specificiy (the ability to classify non-cases with a minimum of false positives) Table III presents this informa

*The unsta dardized discriminant coefficients and cut points f r the discrimin nt analyses may be obtained on request.

Table III Classification accuracy of five different risk factor orientations

Actual group	*Predicted*									
	Clinical		*Epidemiological*		*Psychosomatic*		*Combined*		*Clin. + Epi.*	
	+	−	+	−	+	−	+	−	+	−
Vessel disease +(83)	71	12	54	29	58	25	74	9	73	10
No vessel disease −(16)	1	15	4	12	6	10	0	16	0	16
Sensitivity	.86		.65		.70		.89		.83	
Specificity	.94		.75		.63		1.00		1.00	
% Over all accuracy	87%		67%		69%		91%		90%	

tion for each of the five discriminant analyses. The risk factor orientations on the whole have a higher *specificity than sensitivity, that is, they* are more useful in ruling out the presence of disease than ruling it in. It should be noted that the sensitivity could have been improved by moving the discriminant "cut point"; the cost of this, however, would be a decrease in the over all accuracy.

In the cases of the total combined and the combined clinical and epidemiological orientations, the discriminant analyses accurately classified *all* of those subjects found to be free from vessel disease. The clinical orientation alone had *a specificity of 0.94, or in other words* diagnosed "false positive" only 6 per cent of the time. The sensitivity (ability to recognize "true cases") was rather lower than specificity for each orientation. The clinical orientation had a sensitivity of 0.86, meaning it made a "false negative" diagnosis 14 per cent of the time. Little increase in sensitivity was gained by combining the theoretical orientations.

Finally, the over all predictive accuracy was studied. The percentage of patients accurately diagnosed was compared across orientations and is listed at the bottom of Table III. Again, the clinical orientation was most accurate; little was gained by combining other orientations with it.

Discussion

In this sample the clinical perspective is the best single discriminator for predicting the presence versus the absence of coronary artery disease. Using five simple variables, the clinical equation is accurate 87 per cent of the time. However, before one relegates the epidemiological, psychosomatic and combined approaches to superfluity, one must recall the sample derivation used in this study. It is a clinical sample; that is, the patients already have some clinical evidence of CAD and are being treated at a specialized university center for their illness. Nevertheless, the sample included a substantial proportion of patients (16 per cent) who were found free of vessel disease at the time of catheterization. The sample was adequate in size to allow statistical comparisons of such patients with and without coronary artery occlusive disease.

Although the epidemiological orientation yielded a significantly accurate prediction, it did not match the significance of the clinical orientation. How can we understand the comparatively poor showing of the epidemiological orientation? There is considerable evidence as to the importance of these risk factors.[10,11] Such factors might have great prognostic ability in the general population; however, the situation faced by the clinician is very different from that of the epidemiologist. Our sample is derived from clinical practice, that is, the patients are studied because they have some abnormality. In this setting, the patient's past exposure history dims in relevance compared to his current signs and symptoms. The lower predictive ability of a Framingham style orientation is not to say that such factors are irrelevant: recent study shows that with increased exposure to such risk factors there is an increased incidence of coronary artery disease.[1,19] Our study also demonstrates that such an epidemiological orientation is able to predict coronary artery disease; however, it misdiagnoses one third of the sample.

It is possible that other measurements of risk

factors could have improved the accuracy of the epidemiological orientation We have data on the patient s current triglyceride and cholesterol levels possibly many of our patients have lowered their lipids through diet or medication If such were the case a variable such as *history* of elevated lipids might be expected to yield better predictive power

How can we understand the comparatively poor predictability of the psychosomatic orientation? One possibility is that different measurements for these variables would have been more useful Our measure for Type A behavior was the JAS (Jenkins Activity Survey) the JAS has come under recent criticism as having limited validity compared to the semi structured interview for assessing Type A personality Our stress inventory assessed the patient s recent stress accumulation over the past 4 months We chose this interval as the SRE (Schedule of Recent Events) has decreasing validity the more the subject has to look back over his life experience A stress measure more sensitive to chronic exposure would perhaps have been a better choice in the study of a mediator for coronary atherosclerosis Similar criticisms may be against our choice of the POMS (Profile of Mood States) for anxiety depression anger and fatigue The POMS assesses recent mood states (the past couple of days) as opposed to enduring traits One might expect that the long term exposure to anxiety and depression may have its physiological consequences in engendering coronary artery disease but that short term exposure to such factors is unlikely to be associated with coronary artery disease itself The recent work of Zyzanski and colleagues' would suggest that the traits of anxiety and depression as measured by MMPI derived scales are significantly associated with the extent of coronary artery disease

Subject to the above questions concerning the appropriateness and validity of our psychosocial measures one could postulate that rather being relevant to the anatomical extent of coronary artery disease psychosocial factors may be relevant to other dimensions of cardiac pathophysiology such as arrhythmias

Although the combined approach is very successful at discriminating the presence or absence of vessel disease it entails cumbersome mathematics One loses little information by deleting the psychosomatic variables from the combined orientation i e the combined clinical and epidemiological approaches perform almost as well as the combination of all three approaches The combination of theoretical approaches is particularly helpful in minimizing false positives

We have discussed a statistical procedure for 'modeling the information obtained from cardiac catheterization There are two reasons for doing this One is to ascertain which theory of risk best predicts coronary vessel disease The second is to test whether any of the orientations is sufficiently accurate to guide the decision making process in the clinical evaluation of patients with coronary disease

Using the clinical and epidemiological orientations we found a 90 per cent accuracy in predicting the presence or absence of coronary artery disease However because our sample size is limited and because multifactorial statistical methods are exquisitely sensitive to minor changes in the sample population our findings should be regarded as tentative pending replication If subsequent studies discover the same high predictive accuracy then this approach may prove useful in deciding on the need for coronary angiography in the individual patient

Conclusion

Different risk factor theories were compared as to their ability to predict the results of coronary angiography The clinical orientation produced the most significant discriminator followed by the epidemiological orientation which was also significant in predicting the presence or absence of vessel disease The psychosomatic orientation was not a significant discriminator by itself Combining the clinical and epidemiological orientations yielded even more accurate equations but the further addition of the psychosomatic orientation added little

Summary

This study compares the ability of various risk factor combinations to predict the extent of coronary artery disease found on coronary angiography

Risk factors were measured in 99 patients prior to coronary angiography Clinical epidemiological psychosomatic and combined orientations were compared as to their ability to predict angiography results

The clinical orientation was the most successful in predicting vessel disease ($p < 0001$) followed by the epidemiological model which was also successful ($p < 03$) In contrast psychosomatic factors were not accurate predictors of vessel disease By combining all of the orientations the accuracy of prediction is improved

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Pervenous retrieval of embolized catheters from the right heart and pulmonary arteries

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The majority of embolized or retained catheter fragments requiring removal from the right heart or pulmonary arteries are inadvertently severed infusion cannulas Embolization has also been reported of the distal catheters of cerebral ventriculo caval (Holter) systems used to relieve hydrocephalus by means of a catheter system connecting the cerebral ventricles with the jugular veins or the superior vena cava [1 2] Fragments of pacing electrodes have also been retained [1 3] Their removal required cardiotomy or pulmonary arteriotomy prior to 1964 when Thomas and associates[6] recovered a fractured segment of a guide wire from the right atrium and inferior vena cava using a bronchoscopic forceps In 1967 Massumi and Ross successfully used a wire snare to remove a polyethylene catheter fragment and further development of this method was later reported by Curry [8 9] Tatsumi and Howland used it to remove a Holter catheter in 1970 Other successful techniques that use venous catheterization and avoid direct surgical removal have since been described and include the use of a ureteral stone catcher[1] or a cardiac bioptome[1 16] for direct removal In addition a variety of hook devices[1] or balloon catheters have been used either to withdraw catheters completely or move them to a more peripheral site for direct snaring The variety of pervenous retrieval techniques that have been reported probably indicate lack of uniform success of any one As unsuccessful cases are rarely published [19] it is difficult to have a perspective of their limitations This report therefore describes the total recent experience of this center which includes the first successful removal of a non visualized catheter from the right heart and an improvement of previously described hooking methods with the use of a Judkins left femoral coronary angiographic catheter

Case reports

Case 1 A five year old boy underwent insertion of a right cerebral ventriculo caval shunt for hydrocephalus After 10 days the radiolucent caval catheter embolized to the right pulmonary artery and was removed via thoracotomy A new caval catheter was inserted Three years later shunt revision which required the insertion of a connector to the same caval catheter was performed After a fall at the age of 19 the patient returned with shunt failure and a chest radiograph showed the barely radiopaque distal catheter in the superior vena cava to be dislocated from the connector in the neck (Fig 1*A*) At exploration the catheter fragment was palpable within the internal jugular vein but could not be removed A new distal catheter was introduced via the right external jugular vein After operation initial radiographs and tomography showed the original caval catheter to have embolized but they failed to locate its site Finally a soft chest radiograph demonstrated it in the right lower lobe (Fig 1*B*)

Venous catheterization retrieval was undertaken in view of the previous thoracotomy and in spite of its radiolucency on fluoroscopy Under local anesthesia an 8F Teflon Curry retrieving catheter* containing a looped 300 cm 0 021 inch

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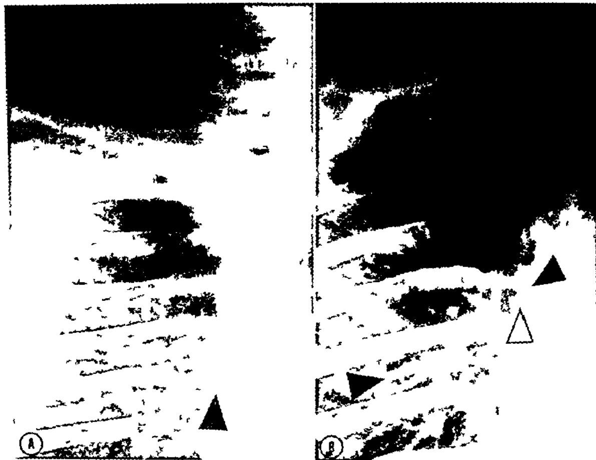


Fig 1 A and B Case 1 A Distal Holter catheter just visible in the superior vena cava and dislocated from connector in the neck. B Same catheter embolized to the right lower pulmonary artery (*solid arrows*) and new easily visualized Holter catheter in superior vena cava (*open arrow*)

Curry wire snare with a flexible mid segment* was inserted via a right saphenous vein cut down Five thousand units of heparin were infused Poor torque control did not allow manipulation beyond the right ventricle The looped wire snare was therefore inserted into a 7F Goodale Lubin woven Dacron catheter† with a flushing adaptor which was readily advanced to the main left and right pulmonary arteries Retrieval of the invisible fragment was attempted by tightening the loop in various positions and by withdrawal to the main pulmonary artery After several attempts a run of ventricular tachycardia suggested successful snaring the Holter catheter causing right ventricular irritation The snaring catheter was removed with a 10 3 cm segment of Holter catheter retained in the snare The saphenous vein was repaired and recovery was uneventful

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Case 2 A 45 year old male first presented wit epilepsy due to hydrocephalus from congenita aqueduct stenosis A right cerebral ventricul caval shunt was inserted the caval catheter wa passed via the right internal jugular vein to th superior vena cava The patient was maintaine on anticonvulsant therapy with improvement bu presented 20 months later with shunt failure an impaired consciousness At exploration a blocke proximal catheter was replaced but the cava catheter distal to the Holter valve was intac Progress after operation was slow with persisten dystonic neck movements and after three week he developed cerebrospinal fluid leak A che radiograph showed that the caval catheter ha embolized with the distal end in the left uppe lobe pulmonary artery and the proximal end i the low superior vena cava (Fig 2A) A ne catheter was inserted

The following day under local anesthesia a 9 Cournand catheter was inserted through a percu

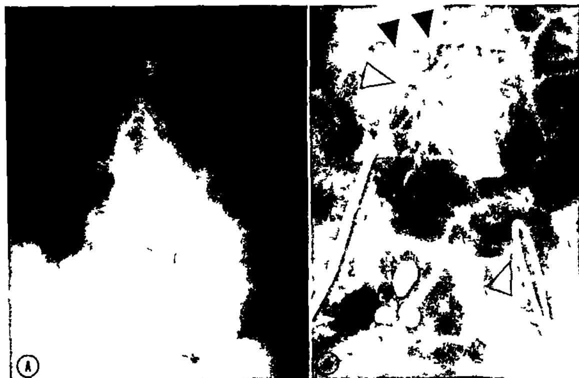


Fig 2 A and B Case 2 *A* Embolized Holter catheter extending from superior vena cava to left pulmonary artery *B* Embolized Holter catheter (*solid arrows*) hooked by left Judkins catheter in left iliac vein and by wire snare in right iliac vein (*open arrows*)

taneous sheath into the right femoral vein With a 300 cm 0 021 inch Curry wire looped inside this catheter unsuccessful attempts were made to snare the Holter fragment in the superior vena cava and the left pulmonary artery A 7F Judkins left coronary angiographic catheter with a 4 cm tip curve* was inserted over a Teflon coated guide wire into the left femoral vein This catheter was readily positioned in the right ventricle and was hooked around the mid point of the embolized Holter catheter by removing the Teflon guide wire The looped Judkins catheter was withdrawn without opening to the left common iliac vein with the hooked Holter fragment retained The wire snare previously inserted via the right femoral vein was readily applied to one end of the Holter catheter in the inferior vena cava (Fig *2B*) The Judkins catheter was then straightened by re insertion of the Teflon guide wire and then withdrawn The snared fragment could not be withdrawn through the percutaneous sheath and both were removed together percutaneously A 36 1 cm distal Holter catheter was folded by the snare into the Cournand catheter The procedure was complicated by a right femoral vein thrombosis treated with oral anticoagulation The patient s neurological state improved and further progress was uncomplicated

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Case 3 A 45 year old male with Tetralogy of Fallot was admitted with sudden onset of breathlessness and diminution of consciousness He was deeply cyanosed polycythemic and dehydrated with severe clubbing and acidosis To correct these metabolic derangements in the possible presence of pulmonary embolism or pulmonary arterial thrombosis estimation of central venous pressure was considered necessary During insertion into a subclavian vein using a percutaneous technique a cannula was severed by the introducing needle Radiographs showed its embolization to the right ventricle but prior to starting retrieval and diagnostic cardiac catheterization the fragment passed into the pulmonary artery Under local anesthesia retrieval was attempted using the Curry set consisting of an 8F Teflon catheter and a 300 cm 0 021 inch looped guide wire It was necessary to change the Teflon catheter for an 8F Cournand woven Dacron catheter to achieve

passage through the stenosed right ventricular outflow tract across a systolic pressure gradient of 80 mm Hg Not surprisingly manipulation within the pulmonary arteries was limited and snaring was not possible The patient proceeded immediately to surgery where the cannula together with thrombus was successfully retrieved from the right pulmonary artery Total correction of the congenital defects was performed with subsequent recovery

Case 4 A 54 year old man developed pacemaker system failure due to electrode fracture 17 months after insertion of an endocardial pacing system for syncope due to sinus node disease During attempts to remove the fractured catheter it severed completely as its distal tip was firmly adherent to the right ventricular apex The proximal end came to lie in the right ventricular outflow tract where it caused persistent ventricular arrhythmias Under local anesthesia a 300 cm 0.021 inch steel guide wire looped inside a 7F Cournand catheter was inserted into the RV via the right antecubital vein but snaring in the right ventricle was unsuccessful A 7F 4 cm tip curve Judkins left femoral coronary angiographic catheter was then inserted percutaneously via the right femoral vein The catheter was successfully looped around the severed pacing electrode in the right ventricle by removal of the guide wire as in Case 2 The proximal end was then easily withdrawn into the right atrium where it was successfully snared by the previously inserted wire loop However the distal tip of the electrode could not be pulled free from its firmly fixed position and the attempt at retrieval was abandoned after the free end has been positioned in the inferior vena cava using the Judkins catheter A new pacing electrode was implanted and there have been no arrhythmias or complications up to one year later

Discussion

Embolization of the distal segment of a Holter cerebral ventriculo atrial shunt to the heart or pulmonary arteries is a rare complication The first successful removal of such an embolism was in 1963 from the right ventricle of a four month old infant by inflow occlusion under hypothermia Further cases requiring direct surgical removal were reported prior to 197[illegible] when Tatsumi and Howland using a loop snare successfully retrieved a dislodged Holter catheter from the right atrium of a four month-old child Previously however, Massumi and Ross in 1967 used a snaring device to retrieve an infusion catheter fragment from the right atrium and in 1969 a similar system with a wire loop was described by Curry[8,9] Successful snare retrieval from the pulmonary arteries was first described by Miller and colleagues[11] in 1970

Retrieval of venous infusion catheters has been reported more frequently than retrieval of Holter catheters dislocation of the latter has mainly occurred in infants and children below the age of three and has probably been related to growth possible explanations have been discussed by Tatsumi and Howland[1] The loss of continuity occurring in these two adults is clearly due to factors other than growth The caval catheter of Case 1 became detached after a fall and in Case 2 the catheter was observed intact and attached to the Holter valve at the time of surgery 2 years after implant and prior to detachment This suggests that mechanical factors and in particular surgical exploration with subsequent dystonic neck movement accounted for embolization Although this is a rare problem the use of a cement bonded flange at the site of venous entry should be considered together with bonding to the Holter valve

It is apparent from the varied techniques described in the last ten years and from the four cases reported herein that there is no single method which offers a high chance of successful retrieval in every case A repertoire of possible methods is desirable they may be divided into two basic processes The first exemplified by the wire snare used in this study initially described by Massumi and Ross[7] is preferable as the fragment is actively grasped and withdrawal is then immediate and straightforward Variations on this theme include a nylon or silk loop[2] endoscopic forceps[6,18] [8,2] a ureteric stone catcher[1,5] and the cardiac bioptome[15,16] Frequently however it is not possible to pass a loop over the ends of the catheter fragment because they abut against chamber or vessel walls or because the loop cannot be maneuvered into the appropriate plane this latter problem also causes failure with endoscopic forceps or the bioptome Here a second method such as the use of a hook or balloon becomes necessary to either completely

remove or partially withdraw the embolized catheter to a site where direct snaring or grasping may be achieved Thomas and co workers in 1964 in the original report were able to displace with a catheter a lost segment of guide wire down the inferior vena cava where it came within reach of endoscopic forceps Rossi in 1970 [7] used a hook shaped Kifa catheter to effect complete withdrawal of a lost catheter McSweeney and Schwartz in 1971[1] used a Muller deflecting system and Broomfield used a hooked guide wire in the same manner Gerlock described a combined technique where a hooked Kifa catheter was used to withdraw a fragment to the iliac vein where a looped wire snared the end for complete withdrawal A balloon catheter has been used for a similar purpose

The technique used in Cases 2 and 4 was similar to that of Gerlock but the left Judkins coronary catheter with its smooth 4 cm by 2 cm preformed closed loop had advantages over the Kifa catheter or looped wire Withdrawal of a guide wire from the Judkins catheter allowed complete encirclement of the embolized catheter fragment more certain withdrawal down the inferior vena cava and easier positioning of the end of the catheter fragment for snaring with a wire loop at the orifice of the right common iliac vein Although final withdrawal of the pacing electrode fragment was not effected in Case 4 the use of the Judkins catheter did allow ensnarement and subsequent location of the fragment s free end to a position where it was not a mechanical focus for arrhythmias As retrieval of catheter emboli will invariably be performed in cardiological laboratories the use of the left Judkins coronary catheter has the additional advantage of ready availability it is stocked in most laboratories and most operators are familiar with its use The only special equipment required therefore to perform retrieval procedures are a 300 cm 0 021 inch guide with flexible mid segment and a flushing adaptor The commercially available Curry retrieving sets employ the guide wire within a Teflon catheter such catheters have relatively poor torque control and manipulation beyond the right ventricle has not always been possible In Cases 1 and 3 manipulation into the distal pulmonary artery was essential and was achieved by the previously unreported substitution of a woven Dacron catheter of identical dimension the characteristics of which will be familiar to all catheterization staff

Although the catheter fragment in Case 1 was located in the right pulmonary artery by means of a soft radiograph it was not visible on fluoroscopy In spite of this difficulty catheter retrieval was undertaken especially since thoracotomy had been necessary 15 years previously This is the first time that successful withdrawal of a radiolucent fragment from the right heart has been accomplished although it has been described in systemic arteries [3] Since that time we have successfully used xerography [3] to eliminate the possibility of radiolucent catheter fragment embolism in a further patient and believe that this form of radiography may here be especially valuable for the location of radiolucent catheters

The development of venous thrombosis in the right leg of Case 2 after percutaneous removal of the Holter catheter may have been due to thrombus formation around the catheter fragment which stripped off during percutaneous withdrawal This complication favors the use of saphenous vein cut down where there might be a greater chance of removing thrombus with catheter Retained catheter fragments are a known source of thrombus and this is one indication for their removal [1] Although it might be advisable to anticoagulate from the time the incident is recognized throughout the retrieval procedure and possibly for a period afterwards catheters have been known to penetrate the myocardium especially the atrium causing tamponade [3] This constitutes another indication for their removal and was the reason for avoiding anticoagulants in Cases 2 and 4 It therefore might be advisable to anticoagulate only after the procedure This decision must be made with knowledge of the site and type of the catheter the time elapsed since the accident and the method of retrieval and should not necessarily be recommended in all cases

It is not possible to obtain from the literature information regarding the frequency of successful catheter retrieval as presumably most unsuccessful attempts are unreported However the ensnarement of three of the four catheters in this complete series should give encouragement to those faced with similar situations Although the need for retrieving embolized catheters may be lessened with improved design of intravenous

infusion and monitoring catheters the possibility of accidental loss will always exist and laboratories should be able to offer the facility The need for specialized equipment is minimal Laboratories have within their stock most of the necessary devices and need supplement it with only a wire snare and flushing adaptor It is equally important that those who may be called upon to attempt retrieval should be familiar with the techniques and their limitations and the experience of others

Summary

Successful removal of embolized or retained catheter fragments from the right heart was achieved in two out of four patients using pervenous catheter techniques For the first time a fragment radiolucent on image intensification was retrieved from the right pulmonary artery using a wire snare In a second case a hook loop was made in the right ventricle with a Judkins left femoral coronary angiographic catheter which has advantages over previously described hooking devices to withdraw a fragment to the iliac vein for subsequent snaring Failure of retrieval occurred only in specially difficult circumstances when a catheter embolized to the pulmonary artery of a Tetralogy of Fallot and when in spite of successful ensnarement a fractured electrode was firmly adherent to the right ventricular apex Successful pervenous retrieval may require a combination of techniques which move or dislodge such as a hook or balloon combined with those which ensnare such as a wire loop or bioptome Using such techniques with minimal additions to standard equipment retrieval procedures can be offered as a routine cardiac catheterization service with a high rate of success

We would like to thank Professor V Logue for referring Case 1 Professor R W Gilliatt for referring Case 2 and Dr R W Emanuel and Mr N Shannon for their advice

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Adrenal cortico-medullary junction necrosis a morphologic marker for hypotension

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A variety of forms of adrenal necrosis have been described tubular degeneration of Rich[1] infarction Waterhouse Friedrichsen syndrome[2] hemorrhage and sepsis In these forms of pathology necrosis is widespread in the cortex The tubular degeneration described by Rich for example originates in the zona fasiculata as a result of intense adrenocorticotropic hormone (ACTH) stimulation[3] The pathogenesis of other forms of necrosis is varied but cell destruction has not yet been specifically associated with the cortico medullary junction We have been impressed at autopsy with the frequent occurrence of adrenal cortico medullary dissolution particularly with a history of shock. The present study was undertaken to determine the relationship of this lesion to hypotension

Materials and methods

A review was performed of 100 consecutive patients listed in the autopsy files of The Johns Hopkins Hospital Patients were included in the study if relevant clinical information and histological material were available The liver kidneys and adrenals were examined for centrilobular necrosis (CLN) acute tubular necrosis (ATN) and cortico medullary junction necrosis (CMJN) respectively without prior knowledge of the clinical history of each case ATN was considered present if the tubules and Bowman s space

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Table I The association of clinical hypotension with pathologic lesions

Incidence of clinical hypotension	46/100	4[illegible]
Incidence of corticomedullary junction necrosis adrenal (CMJN)	44/100	44%
CMJN and hypotension	38/46	83%
CMJN without hypotension	6/54	11%
Incidence of acute tubular necrosis kidneys (ATN)	39/100	39%
ATN and hypotension	35/46	[illegible]
ATN without hypotension	4/54	7%
Incidence of centrolobular necrosis liver (CLN)	16/100	16%
CLN and hypotension	1[illegible]/46	[illegible]
CLN without hypotension	4/54	7%

$p < 0.001$ $p < 0.05$ by the chi square test.

were dilated and leukocytosis occurred in the vasa recta These three findings particularly the leukocytosis have been specifically associated with ATN[4] CLN was defined as simply the presence of necrotic cells about the central veins. CMJN was determined from the finding of necrotic or pyknotic cells distributed strictly at the cortico medullary junction (Fig 1) Necrosis of the adrenal cortex or medulla was not considered in this lesion unless it appeared as an obvious extension of junctional necrosis Autolysis of the adrenal cortex was readily separated from CMJN since in the autolyzed adrenal cortex cells from all layers are similarly involved

The clinical summaries of each of the autopsy cases were reviewed for evidence of hypotension and acute renal failure The criteria defining a hypotensive episode included repeated systolic blood pressures below 80 mm Hg in previously normotensive or hypertensive patients or when the words hypotension hypoperfusion or shock were used to describe a clinically signifi

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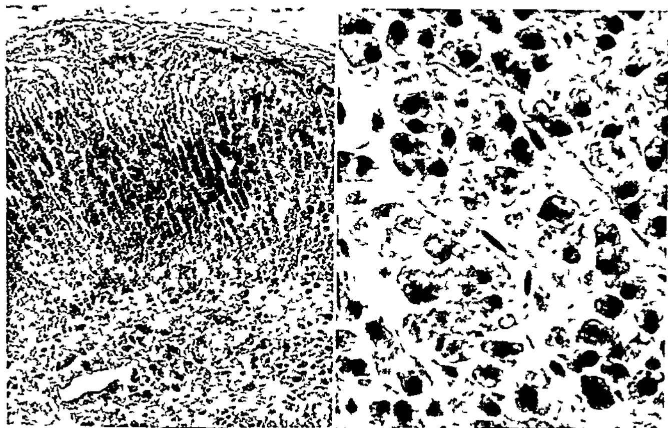


Fig 1 *Left* Adrenal cortex showing well preserved zona glomerulosa and fasciculata but coagulative necrosis of the zona reticularis at the cortico-medullary junction The patient suffered severe hypotension prior to death. (Hematoxylin and eosin original magnification × 5) *Right* Necrosis of adrenal cortex at cortico-medullary junction (Hematoxylin and eosin original magnification ×750)

cant episode Agonal hypotension or episodes consisting of a single low blood pressure determination were excluded Thus the clinical assessment of the patient at the time of fall in blood pressure was the foremost criterion defining hypotensive episodes and in most patients had occurred some hours prior to death Renal failure was considered to have occurred secondary to hypotension whenever oliguria or acute renal failure had been diagnosed and there was no history of other likely causes of renal failure

Results

The incidence of clinical hypotension and the pathologic lesion and the frequency of occurrence of each lesion in relation to hypotension is shown in Table I In the 100 patients studied clinical hypotension or renal failure as a result of hypotension was present in 46 per cent CMJN was present in 38 out of the 46 cases (83 per cent) with hypotension compared to 35 (76 per cent) for ATN and 12 (26 per cent) for CLN When hypotension had not been noted clinically CMJN occurred in 11 per cent of the cases compared to 7 per cent for ATN and 7 per cent for CLN Six other patients had CMJN but no record of hypotension or acute renal failure It is possible that hypotension occurred in those patients also but had escaped clinical note

Table II The association of CMJN with ATN and CLN

CMJN and ATN	26/39	66%
CMJN without ATN	18/61	30%
CMJN and CLN	3/12	20%
CMJN without CLN	41/84	49%

$p < 0.001$ not significant by the chi-square test.

Aside from the direct clinical correlation of hypotension and renal failure with cortico medullary junction necrosis CMJN occurred in 66 per cent of the cases showing ATN (Table II) but only in 20 per cent of cases with CLN Only 30 per cent of the cases of CMJN occurred without ATN

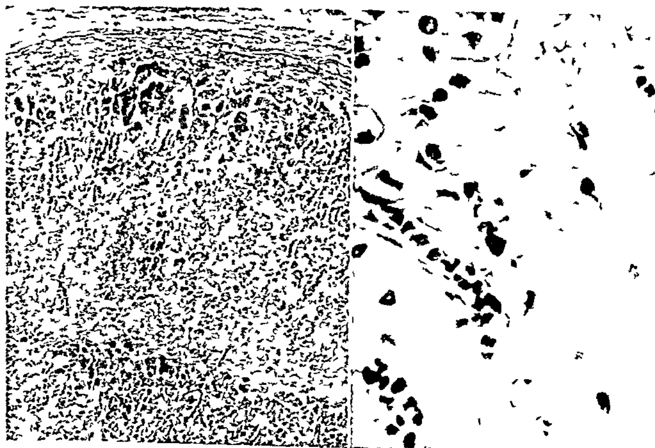


Fig 2 Left Cortico medullary junction fibrosis in a patient who had suffered an episode of severe hypotension in the past (Hematoxylin and eosin original magnification ×75) *Right* Fibrous tissue replaces the cells normally present at the cortico-medullary junction (Hematoxylin and eosin original magnification ×750)

but nearly half (49 per cent) of CMJN was not associated with CLN Therefore the hypotensive episodes associated with CMJN and ATN were significantly correlated The lesions did not occur in separate patient groups but largely overlapped and thus suggested a similar physiological basis of necrosis in the two organs The association of CMJN with centrolobular necrosis (CLN) was not significant

In four cases patchy fibrosis occurred within the cortico medullary junction with no evidence of necrosis (Fig 2) This suggested the possibility that CMJN occurred in the past and subsequently healed leaving a fibrotic scar Two of these patients had documented histories of myocardial infarcts and the others had had major surgery Though the clinical summaries did not provide evidence of a proven hypotensive episode both surgery and myocardial infarcts may be associated with transient periods of hypoperfusion

Discussion

The vascular architecture o the adrenal gland may compromise the abilit of the ce f the cortico medullary junction to react to stre From three to 50 arteries pierce the adren capsule and distribute blood to the sinusoid The sinusoids become confluent at the cortic medullary junction and form a venous plex The cells at the junction are farthest remov from incoming arterial blood In addition duri times of stress as in a hypotensive episode th metabolism and oxygen demands of the adren cortical cells increase markedly as a result ACTH stimulation Hence with the double disa vantage of decreased oxygen supply and increase oxygen demand the junctional cells may b susceptible to hypoperfusion injury The correla tion of cortical medullary junction necrosis wit acute tubular necrosis is further supportin evidence for the role of hypotension in giving ris to the adrenal lesion The active metabolism o the renal tubule cells places a similar limit on cel survival during hypoperfusion

In addition to the sensitivity of CMJN as a marker for hypotension it has the advantage o being a diagnosis which may be made readily The criteria used to diagnose acute tubular necros

are rather accurate as the data show However when leukocytosis of the vasa recta has not yet occurred the vague criteria of Bowman s space and tubular dilatations are subjective assessments made with difficulty Thus the diagnosis of CMJN requires only identification of necrosis or pyknosis of junctional cells and provides a useful morphological marker for hypotensive episodes It is of interest that CMJN occurred commonly in association with ATN but not with centrolobular hepatic necrosis These relationships perhaps reflect a reflex vasospasm of the arterial supply to the kidney and adrenal during severe bouts of hypoperfusion whereas hepatic necrosis may be less a function of reflex vasoconstriction as of sustained portal venous hypoperfusion

Hypotension induced necrosis of the adrenal cortico medullary junction may be of importance in some patients If the patient is anticoagulated there may be hemorrhage into the necrotic zone after re establishment of blood flow Severe bilateral adrenal hemorrhages with probable adrenal insufficiency have been observed in such anticoagulated patients who have survived episodes of transient hypoperfusion[6] In most patients who survive episodes of hypotension with associated cortico medullary junction necrosis it is probable that the lesion heals as a fibrotic scar such as was observed in four patients in this study Thus while adrenal cortico medullary junction necrosis is in itself probably of no functional significance it provides a pathological marker for hypotension and in occasional patients may be the source of adrenal hemorrhage

Summary

There have been many ideas on the pathogenesis of adrenal necrosis to explain forms of adrenal insufficency and hemorrhage The physical separation of the cortex from medulla of the adrenal gland at autopsy and its association with shock has led us to the hypothesis that transient hypoperfusion results in necrosis at the cortico medullary junction (CMJ) In a review of 100 consecutive autopsies cortico medullary junction necrosis was correlated with acute tubular necrosis of the kidney and centrilobular necrosis of the liver lesions compatible with hypoperfusion Clinical evidence of hypotension and acute renal failure were documented from the clinical summaries of the autopsies and were compared with the occurrence of the three lesions Adrenal CMJ necrosis was found to occur in 44 per cent of the cases In 83 per cent of the cases with hypotension or acute renal failure CMJ necrosis was present whereas acute tubular necrosis was present in only 76 per cent of those cases Adrenal cortico medullary junction necrosis may thus be construed as morphologic evidence of hypotension

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A reappraisal of the clinical features in acute and chronic rheumatic heart disease

Etiological implications

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It has been suggested that viruses and similar organisms may be responsible for some cases of acquired valvular heart disease [1,2] The tradition al view however is that virtually all cases are rheumatic Unless one accepts Pearce s propos al[3]—that viral-bacterial synergism may be involved—these theories are mutually exclusive It follows that if viruses are a significant cause of acquired valvular heart disease the traditional explanation must be incorrect

The fundamental tenet of the traditional theo ry is that all acute valvulitis and therefore subsequently all chronic acquired valvular heart disease is due to rheumatic fever As there is no specific diagnostic test for rheumatic fever the validity of this claim can only be assessed indi rectly For example if all cases of acute valvulitis have a common etiology they should either have similar clinical features or fit into a definable clinical spectrum and in chronic valvular disease the pattern of valve involvement should not be significantly affected merely by the presence or absence of a rheumatic history In either situation (acute valvulitis or chronic valvular disease) the presence of a subgroup which does not conform with the group as a whole might be taken as evidence that the atypical cases have a different etiology In the studies described below the clini cal features of acute valvulitis and of chronic acquired valvular heart disease have been assessed to discover if the assertion of a sin (rheumatic) etiology for either group is justifi

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First study clinical features in acute valvulit

Patients and methods Case records of children who convalesced at the Sheffield Rhe matic Hospital School between 1947 and 19 have been analyzed These hospital recor provided data for the U S /U K co operative tr of treatment for rheumatic fever (Joint Workin Party report 1965[4]) case notes were detailed a diagnostic criteria were uniform For the purpose of the present study the diagnoses of polyarthri tis arthralgia chorea and carditis were mad retrospectively on the basis of the definitio s u the revised Jones criteria [5] Isolated carditis wa diagnosed when carditis occurred in the absen of chorea arthritis or arthralgia The following data for each patient were noted age and sex and the presence of subcutaneous nodules erythema marginatum, pericarditis cardiomegaly or car diac failure Details of heart murmurs refer to murmurs present when the patients were discharged from convalescence this permits comparison with the findings of Bland and Jones[6] whose study of the natural history of rheumati carditis is the most comprehensive available and who followed this practice

Preliminary analysis of clinical features indi cated differences between isolated carditis and carditis accompanied by polyarthritis Those with polyarthritis were therefore further analyzed in subgroups to determine if some of them had features not common to the group as a whole but which could explain the peculiarities of the isolated carditis group The rationale for these subgroups was that each should emphasize one

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particular feature which at different times has been held responsible for the severe nature of isolated rheumatic carditis This has been variously ascribed to an inverse relationship between severity of joint pains and of carditis the relative youth of patients with isolated carditis and the prolonged often relapsing nature of the illness Data from patients with joint pains have therefore been analyzed in the following subgroups

Group 1 All patients with polyarthritis

Sub groups

1A Patients with arthralgia

1B Patients with polyarthritis less than nine years of age at the time of onset of symptoms

1C Patients with polyarthritis and cardiomegaly (A diagnosis of cardiac enlargment was accepted if the clinical impression was supported by radiological evidence)

1D Patients with recurrence of polyarthritis or chorea (one or more documented previous attack)

If any of these factors including the severity of carditis per se is responsible for apparent peculiarities of isolated carditis when compared with the polyarthritis group as a whole it should be exposed when the latter group is subdivided in the manner shown above Some cases qualified for and are included in more than one sub group

In addition to analyzing records of patients with polyarthritis and arthralgia two other groups were defined

Group 2 Chorea

Group 3 Isolated carditis

Results

Table I summarizes the clinical features of 248 children treated for acute rheumatic fever The incidence of the various manifestations and complications is comparable to previous reported series[8] Details of clinical features in the groups and subgroups defined above are shown in Table II in absolute figures and bracketed as percentages of the total number in the respective group or subgroup

Group 1 All patients with polyarthritis One hundred and thirty five cases average age 11 4 years 76 males 59 females Subcutaneous nodules occurred in 11 1 per cent and erythema marginatum in 16 per cent Four per cent had pericarditis 35 per cent had cardiomegaly and 4 per cent had an episode of cardiac failure Forty eight per cent had significant heart murmurs when discharged from hospital each had a mitral systolic murmur Twenty per cent in addition had an aortic early diastolic murmur 12 per cent had a mitral diastolic murmur The combination of mitral systolic and mitral diastolic murmurs (without an aortic diastolic murmur) occurred in only seven of the 135 cases

Table I Clinical features in 248 patients treated for acute rheumatic fever

	Number	*Percentage of total*	
Total number of patients	248	100	
Arthritis	135	54 4	70 1
Arthralgia	39	15 7	
Chorea	49	19.8	
Isolated carditis	25	10 1	
Specific features			
Subcutaneous Nodules	17	6 8	
Erythema marginatum	25	10 1	
Pericarditis	13	5.2	
Cardiomegaly	77	31	
Aortic regurgitation	36	14 5	
Normal heart at discharge	119	48	
Residual cardiac damage	129	52	

Defined for the purposes of this study as the presence of a cardiac murmur at the time of discharge from hospital, thought by the attending physician to indicate persisting valvular damage

Subgroup 1A Patients with arthralgia Thirty nine cases average age 10 9 years 17 males 22 females The clinical features were similar to those in Group 1 Carditis was not more severe as judged by the incidence of cardiomegaly cardiac failure and the number leaving hospital with a clinically normal heart Murmurs present when discharged from convalescence were also as in Group 1

Subgroup 1B Patients with polyarthritis aged less than 9 years Thirty seven cases average age 7 7 years 13 males 24 females There were no significant differences between this group and the former group

Subgroup 1C Patients with polyarthritis and cardiomegaly Forty eight cases average age 10 9 years 18 males 30 females Carditis was severe Seventeen per cent had cardiac failure and only 8 per cent left the hospital with a clinically normal heart The incidence of subcutaneous nodules was 31 per cent The incidence of pericarditis (9 per cent) was similar to that in the unselected (Group 1) patients The pattern of murmurs present

Table II Selected clinical features in 248 children treated for rheumatic fever (percentages in parentheses)

Group	Cases	Sex		Age at onset	Subcutaneous nodules
		M	F		
1 Arthritis (all cases)	135	76 (56)	59 (44)	11 4	15 (11)
1A Arthralgia	39	17 (44)	22 (56)	10 9	2 (5)
1B Arthritis (all aged <9 years)	37	13 (35)	24 (65)	7 7	3 (8)
1C Arthritis (all with cardiomegaly)	48	18 (38)	30 (62)	10 9	15 (31)
1D Recurrence of arthritis or chorea	80	32 (40)	48 (60)	10 4	10 (1?)
2 Chorea	49	16 (33)	33 (67)	11 0	0 (0)
3 Isolated carditis	25	12 (48)	13 (52)	9 7	0 (0)

Abbreviations and expansions cases = number of cases Age at onset = average age at onset of symptoms MDM = mitral diastolic murm MSM = mitral systolic murmurs AR = aortic regurgitation (aortic early diastolic murmur) Murmurs = murmurs present at time of discharge hospital

when the patients were discharged from hospital was as in the previous groups

Subgroup 1D Patients with previous polyarthritis or chorea Eighty cases average age 10 4 years 32 males 48 females Clinical features were similar to Group 1 However, significantly less patients (13 per cent) left hospital with a clinically normal heart

Group 2 Chorea Forty nine cases average age 11 0 years 16 males 33 females This group followed the established pattern for chorea—female patients predominated over male patients and carditis was relatively mild and uncommon

Group 3 Isolated carditis Twenty five cases average age 9 7 years 12 males 13 females Twelve (48 per cent) were aged less than 9 years The corresponding figure for Group 1 was 16 per cent and for subgroup 1C (with cardiomegaly) it was 24 per cent Carditis was severe—92 per cent had cardiomegaly 24 per cent had cardiac failure and none left the hospital with a clinically normal heart No patient had either subcutaneous nodules or aortic regurgitation (neither did any have erythema marginatum) The incidence of pericarditis was 28 per cent When discharged from hospital 76 per cent had mitral systolic plus mitral diastolic murmurs 20 per cent had only a mitral systolic murmur One patient had an isolated mitral diastolic murmur

Differences between the clinical features associated with isolated carditis and those found in other groups

1 The incidence of combined mitral systolic and mitral diastolic murmurs was significantly higher in the isolated carditis group (19 out of 25) than in any other group or subgroup Compa[red] with subgroup 1D which had the next high[est] incidence of these two murmurs (16 out of 8[0]) $\chi^2 = 27.83$ $p < 0.001$

2 With the exception of subgroup 1C (wh[ich] by definition contained only cases with card[iac] enlargement) the incidence of cardiomegaly [in] those with isolated carditis was significantly hi[gh]er than in the subgroup with the next high[est] incidence (subgroup 1D)—23 out of 25 compar[ed] with 32 out of 80—$\chi^2 = 18.60$ $p < 0.001$

3 The incidence of subcutaneous nodules w[as] significantly lower in those with isolated card[itis] (0 out of 25) than in those with polyarthritis w[ho] had a comparably severe carditis (subgrou[p] 1C)—15 out of 48 $\chi^2 = 9.88$ $p < 0.01$

4 The incidence of pericarditis was significan[t]ly higher in those with isolated carditis than [in] those with polyarthritis (Group 1)—7 out of 2[5] compared with 6 out of 135—$\chi^2 = 16.4$ $p < 0.001$ It was also higher than in those wi[th] polyarthritis and a comparably severe cardit[is] (subgroup 1C)—4 out of 48 $\chi^2 = 5.08$ $p < 0.05$

5 The incidence of aortic regurgitation wa[s] significantly lower in those with isolated cardit[is] than in those with polyarthritis who had comparably severe carditis (subgroup 1C)—0 ou[t] of 25 compared with nine out of 48 $\chi^2 = 5.4$ $p < 0.05$

Note 1 Murmurs present when patient discharged from convalescence Massell an[d] colleagues have shown that it is exceptional fo[r] new murmurs to develop in relationship to acut[e] rheumatic carditis more than three months fro[m] the onset of symptoms In the present study th[e]

Erythema marginatum	*Enlarged heart*	*Cardiac failure*	*Pericarditis*	*Murmurs* *MDM*	*MSM*	*AR*	*Normal heart when discharged from hospital*
22 (16)	48 (35)	5 (4)	6 (4)	16 (12)	[illegible]0 (65)	27 ([illegible]0)	70 (52)
3 (8)	6 (15)	0 (0)	0 (0)	6 (13)	25 (64)	5 (13)	15 (39)
4 (11)	3 (8)	1 (3)	4 (11)	0 (0)	21 (57)	1 (3)	18 (49)
0 (0)	48 (100)	8 (1[illegible])	4 (8)	9 (19)	4[illegible] (88)	9 (19)	4 (8)
6 (8)	32 (40)	10 (13)	6 (8)	16 ([illegible]0)	[illegible] (96)	19 ([illegible]4)	10 (13)
0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	16 (33)	4 (8)	34 (69)
0 (0)	23 (9[illegible])	6 (24)	7 ([illegible]8)	[illegible]0 (80)	[illegible]4 (96)	0 (0)	0 (0)

time between recovery from the acute phase of illness (judged by return of the sedimentation rate to normal) and discharge (when murmurs were recorded) was similar for those with isolated carditis and those with polyarthritis—14 weeks for the former group and 12 weeks for the latter group Thus the different murmurs demonstrated cannot be attributed to the recording of them at a different stage of illness in the two groups

Note 2 Symptoms referable to carditis With one exception patients with isolated carditis were admitted to hospital because of symptoms refer able to the heart—chest pain breathlessness on exertion ankle swelling anorexia cough or vague ill health The exception was a 10 year old boy with murmurs of mitral stenosis and regurgi tation diagnosed at a routine medical examina tion but found to have a low grade fever and a raised sedimentation rate In those with polyar thritis or chorea it was unusual at any stage of the illness for there to be symptoms directly attributable to the heart except when there was cardiac failure pericarditis or cardiomegaly—and not always in this latter group

Second study Valve lesions in acquired valvular heart disease

Patients and methods Three hundred and eleven consecutive patients with valvular heart disease seen at the Northern General Hospital Sheffield were examined questioned and their case records were analyzed Eleven patients with isolated aortic valve disease were excluded as it was impossible to distinguish clinically between rheumatic and non rheumatic cases The remainder had rheumatic heart disease —i e mitral stenosis mitral stenosis with regurgitation mitral regurgitation or mitral plus aortic valve disease Valve lesions were defined by clinical examination supported in the majority of cases by findings at cardiac catheterization and/or cardiac surgery Details of previous rheumatic fever or chorea and of cardiac operations were noted Patients were examined without prior knowledge of these historical facts Four patients were excluded because the history they gave was so vague that it was not possible to decide whether or not they had had rheumatic fever The 296 remaining patients were alloted to one of two groups (1) those with a history of previous rheumatic fever or chorea and (2) those with no history of previous rheumatic fever or chorea Many patients had had cardiac surgery and this obviously altered the auscultatory findings In order to obtain a reasonable assessment of the preoperative state of these patients valves (so that they would be comparable with unoperated patients) two assumptions were made

A A history of mitral valvotomy has been taken to indicate preoperative pure mitral steno sis or mitral stenosis with trivial mitral regurgi tation

B A history of mitral valve replacement has been taken to indicate pure or dominant mitral regurgitation as the probable preoperative valve lesion This assumption is less justified than that made with respect to mitral valvotomy for two reasons first because patients who have calcific mitral stenosis now frequently have elective mitral valve replacement and second because mitral valve replacement is the operation of choice in many patients who have previously had mitral valvotomy

Because of these reservations the incidence of

Table III Age, sex, and numbers submitted to surgery in each group

	Patients with history of rheumatic fever	*Patients with no history of rheumatic fever*
Total number of cases (all with mitral valve disease)	164 (100%)	132 (100%)
Average age	49 4 yrs	49 9 yrs
Female	117 (71%)	115 (87%)
Male	47 (29%)	17 (13%)
Number who underwent surgery	114 (70%)	103 (78%)
Numbers not submitted to surgery	50 (30%)	29 (22%)

Table IV Valve lesions in patients with and without a history of rheumatic fever

	With rheumatic fever history	*No rheumatic fever history*
Mitral valve disease	164 (100%)	132 (100%)
Aortic valve disease	99 (60%)	27 (21%)
Mitral valve disease only	65 (40%)	105 (80%)
Isolated mitral stenosis (in patients not operated upon)	5/50 (10%)	17/29 (59%)

Expressed as a percentage of those not submitted to surgery

pure or dominant mitral regurgitation in the two groups will be based primarily on cases not operated upon the relative incidence of mitral valve replacement will only be quoted for the sake of completion

Results

Two hundred and ninety six patients were studied 164 had a past history of rheumatic fever or chorea and 132 had had neither Details of these patients are shown in Tables III VI By definition all patients had mitral valve disease

Table III shows the sex distribution in the two groups Significantly more patients in the group with no rheumatic history are female—87 per cent as opposed to 71 per cent ($\chi^2 = 10$ ·· $p < 0.01$)

There are significant differences between the groups with respect to the incidence of aortic valve disease and the nature of mitral valve involvement

1 Aortic valve disease is more common in those who had had rheumatic fever (Table IV) 99 (60 per cent) have an aortic valve lesion compared with 27 (21 per cent) of those with no rheumatic history ($\chi^2 = 46.03$ $p < 0.001$) This difference is reflected in the numbers from each group who had aortic valve replacement (Table V) 30 (18 per cent) of the former group and seven (5 per cent) of the latter group ($\chi^2 = 13.23$ $p < 0.001$)

2 Isolated mitral stenosis (i e without significant mitral regurgitation and with no aortic valve disease) is more common in the group with no rheumatic history

a Table IV shows that in patients not operated upon and in whom therefore auscultatory findings could not have been affected by the results of cardiac surgery isolated mitral stenosis occurred in 17 out of 29 (59 per cent) of those with no rheumatic history, but in only five out of 50 (10 per cent) who had ($\chi^2 = 19.24$ $p < 0.001$)

b This difference is also demonstrated by the numbers from each group who had had mitral valvotomy (Table V)—58 per cent as opposed to 35 per cent ($\chi^2 = 11.07$ $p < 0.001$)

3 Mixed mitral valve disease or mitral regurgitation is more common in patients who have had rheumatic fever This is the corollary of paragraph No 2 above since all patients had mitral valve disease and is supported by the figures for mitral valve replacement (Table V) Thirty two per cent of those with a rheumatic history had these signs and only 19 per cent of those with no rheumatic history had had them Sixty-eight per cent of all mitral valve replacements were performed on patients who had had rheumatic fever

4 The higher incidence of aortic valve disease and of mixed mitral valve disease in the group with a rheumatic history is supported by the figures for double valve replacement (mitral plus aortic) (Table V) Fifteen per cent of those who had had rheumatic fever compared with 4 per cent of those with no rheumatic history have had double valve replacement ($\chi^2 = 11.84$ $p < 0.001$)

5 Table VI details operations performed on patients who had only mitral valve disease Mitral valvotomy was performed on 60 per cent of

those with no rheumatic history and in 29 per cent of those who had had rheumatic fever ($\chi^2 = 14.01$, $p < 0.001$) The respective figures for mitral valve replacement are 15 per cent and 34 per cent

Discussion

Previous studies of the clinical features of rheumatic fever and of chronic acquired valvular heart disease have invariably analyzed all cases of acute carditis as a single (rheumatic) group and likewise with respect to chronic valvular disease have grouped patients together irrespective of the presence or absence of a rheumatic history This approach was justified by the widely held belief that all cases of acquired valve disease—acute and chronic—are rheumatic and that therefore the cases studied represented the clinical spectrum of a single disease However any differences between those with and those without an unequivocal rheumatic history would obviously be obscured by this practice In contrast for the purposes of the present study it was postulated that the etiology of those with and those without a clear rheumatic history might be different and that this might result in clinical differences between the two groups

Acute isolated carditis (as defined by the American Heart Association in 1965[5]) is considered to be a severe form of rheumatic carditis The clinical features in such cases should therefore be similar to those in carditis of comparable severity which accompanies rheumatic polyarthritis The first of the two studies described above shows that this is not so as indicated particularly by the different incidence of subcutaneous nodules and of pericarditis in the two groups Furthermore the murmurs present when patients were discharged from hospital were not the same in these groups—mitral systolic plus mitral diastolic murmurs in virtually all of the isolated carditis group a mitral systolic murmur often with an aortic early diastolic murmur in the polyarthritis group

The spectrum of carditis attributed to rheumatic fever is based on studies in which isolated carditis polyarthritis with carditis and cases of chorea have been grouped together as rheumatic carditis On the basis of such studies it appears that the severity of carditis is inversely proportional to that of joint pains [1] that severe

Table V Details of valve surgery

	Patients with history of rheumatic fever	*Patients with no history of rheumatic fever*
Total number of cases	164 (100%)	132 (100%)
Mitral valvotomy (includes patients who subsequently had further surgery)	58 (35%)	76 (58%)
Mitral valve replacement (includes those who also had aortic valve replacement)	53 (32%)	25 (19%)
Aortic valve replacement (includes those who also had mitral valve replacement)	30 (18%)	7 (5%)
Double (mitral plus aortic) valve replacement	25 (15%)	5 (4%)

Table VI Details of valve surgery confined to patients who had only mitral valve disease

	With rheumatic fever history	*No rheumatic fever history*
Total number of cases with only mitral valve disease	65 (100%)	105 (100%)
Mitral valvotomy	19 (29%)	63 (60%)
Mitral valvotomy followed by mitral valve replacement	10 (15%)	7 (7%)
Mitral valve replacement (not preceded by mitral valvotomy)	12 (18%)	9 (9%)
Total mitral valve replacements	22 (34%)	16 (15%)

carditis occurs in the younger patients and is accompanied by an increased incidence of aortic regurgitation pericarditis and subcutaneous nodules [12, 1] These widely accepted observations apply to the patients described in the present study only if they are considered as a single group when the two groups (isolated carditis and polyarthritis with carditis) are examined separately neither conforms to this pattern Isolated carditis which understandably was usually severe was associated with a high incidence of pericarditis but no patient had either subcuta

neous nodules or aortic regurgitation Both of these features were however related to the severity of carditis in those with polyarthritis whereas the incidence of pericarditis was not Although patients in the group with isolated carditis were, on average younger than those with polyarthritis the youngest patients in this latter group did not have a severe carditis

Belief in the existence of an inverse relationship between severity of joint pains and of carditis is important to the traditionally described spectrum of clinical features caused by rheumatic fever for it provides a link between isolated polyarthritis and isolated carditis This inverse relationship was not demonstrated in the present study, arthralgia was not associated with a more severe carditis than was polyarthritis These findings were contrary to those of Feinstein and Spagnuolo [11] whose studies supported and popularized the concept of the inverse relationship described It is clear however from the data which they provide that their conclusions were based on selected case material This is almost inevitable as many mild cases of arthralgia will not reach hospital unless more serious symptoms are produced by for example carditis The size of this hidden group of patients cannot be predicted Presumably the cases described in the present study were a more representative group than those of Feinstein and Spagnuolo

The diagnosis of acute rheumatic carditis is based on the revised Jones criteria [5] Using these guidelines the process of establishing a rheumatic etiology in patients with isolated carditis separates them from those with polyarthritis Confirmation of a rheumatic etiology in isolated carditis requires only the presence of two minor manifestations each of which is non specific In addition some cases of isolated carditis are specifically excluded from the additional requirement of evidence of recent streptococcal infection on the grounds that the initiating infection may have occurred weeks or months before medical advice was sought by which time the ASO titer could have returned to normal This is arguable for Stollerman and associates have shown that following streptococcal infections the ASO titer usually does not return to pre infection levels for six to 12 months Be that as it may the consequence of this exclusion appears to have been overlooked in cases of isolated carditis without an elevated ASO titer or a positive throat swab culture there is no evidence that the illness is in any way related to previous streptococcal infection The observation by Findlay [13] that isolated carditis is preceded by scarlet fever significantly less often than is rheumatic polyarthritis, provides further evidence of a poor correlation between isolated carditis and streptococcal infection Thus the assertion that all cases of acute valvulitis have a common (rheumatic) etiology is without proof The significance of this observation is increased when it is considered in conjunction with the findings above showing that the same cases (those with isolated carditis) are clinically distinct from those with unequivocal rheumatic carditis Furthermore the striking similarity between some documented cases of viral heart disease[15,17] and cases diagnosed as isolated rheumatic carditis suggests an alternative to rheumatic fever as the etiology [18]

The natural history and evolution of chronic rheumatic heart disease has been described by Bland and Jones [8] Twenty years after an attack of acute rheumatic fever those patients who developed established valve lesions most commonly have mixed mitral valve disease or mitral regurgitation and in 60 per cent of cases additional aortic valve disease Pure mitral stenosis (as opposed to mixed mitral valve disease) occurs in only approximately 10 per cent of cases, and even then is usually associated with an aortic valve lesion [19] These findings correspond closely with the pattern of valve involvement shown by the present study to occur in patients who recalled having previously had rheumatic fever This represents the end result of predominantly mild rheumatic carditis for Bland and Jones have shown that 80 per cent of those with initially severe carditis die within 20 years

Patients with valvular heart disease but no history of rheumatic fever had according to the traditional explanation a mild rheumatic carditis which passed unnoticed If this is so their valvular disease should be similar to that described both here and by Bland and Jones in long term survivors of acute rheumatic fever since it also represents the end result of (predominantly) mild rheumatic carditis This however is not the case Patients with valvular disease but no history of rheumatic fever often have pure isolated mitral stenosis and the incidence of aortic valve disease is only 20 per cent

It could be argued that the higher incidence of

aortic valve disease in the group with a rheumatic history is itself evidence that they had a more severe initial carditis and that therefore the two groups are not strictly comparable However even after exclusion of all cases with aortic valve disease from each group the differences in the types of mitral valve disease which these two groups have is still apparent those with no rheumatic history have more frequently had mitral valvotomy indicating a higher incidence of pure or dominant mitral stenosis (*vide supra* point 5 in Results section)

Thus in the case of both acute valvulitis and chronic valvular heart disease two groups of patients with significantly different clinical features can be defined The clinical group into which a particular patient fits is largely determined by whether or not he has had an attack of acute rheumatic fever

The differences between patients with and without a rheumatic history are not only clinical Ward and associates[20, 21] have shown significant differences in the HLA antigen patterns of the two groups implying that they differ genetically antigens A29 and AW30/31 were both significantly more common in the group with no rheumatic history

Patients with acquired valvular disease but no rheumatic history have nevertheless obviously had previous acute carditis However the two distinct patterns of valvular disease described above are difficult to equate with a common (rheumatic) etiology Indeed in patients with no rheumatic history it is purely speculative to claim that the initiating carditis was rheumatic since by definition it passed unobserved The evidence described and reviewed here casts doubt on the rheumatic fever theory of acquired valvular heart disease This and the accumulating evidence which implicates viruses in some cases[1, 2, 3] justifies continued research into other possible etiological agents Alternatively the traditional theory must be modified to explain how two groups of patients with valvular disease of the same etiology and with an initiating carditis of comparable severity have different patterns of valvular involvement

Conclusions

1 Many cases of isolated rheumatic carditis lack proof of a rheumatic etiology Despite this isolated carditis has been incorporated into a spectrum of clinical features attributed to rheumatic fever This practice has obscured significant clinical differences described here between isolated carditis and the carditis which accompanies rheumatic polyarthritis

2 Valve lesions in patients with acquired valvular heart disease are related to the presence or absence of a rheumatic history The differences between the groups are such that it is usually possible to predict from the clinical findings whether or not the patient has had rheumatic fever

3 The different patterns of acute and chronic valvular involvement which have been described being dependent on whether or not the patient has had rheumatic fever suggests that more than one etiological agent may be responsible for what is currently regarded as a single entity—rheumatic heart disease

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Maladie du Roger 1879 A new translation for the centenary

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On October 21 1879 Henri Roger described to the Academie de Médecine the clinical and auscultatory findings in six acyanotic patients with a murmur and the chance autopsy finding of a ventricular septal defect (VSD) in a child whom he had never seen in life[1] He in his own words "immediately applied the finding of morbid anatomy and concluded that the murmur in his acyanotic asymptomatic patients was the pathognomonic sign of VSD

While VSD was well recognized as part of complex congenital heart disease Roger appreciated that unlike cyanotic disease the malformation which bears his name was entirely compatible with a normal life span

Biographical note Henri Roger was a Parisian born in January 1809 He qualified in Paris in 1839 and remained in practice there until his death in November 1891 He was a Knight of the Legion of Honour an Agrége of the Faculty of Medicine and a member of the Academy of Medicine He was also Physician to the Hospitals

According to Labarthe[2] he had a huge practice (as a pediatrician) in which he was wholly absorbed and which left him very little time for desk work. He collaborated with Barth in a Treaty of Auscultation which was first published in 1841 and ran to a number of editions

Translator s note Roger was 70 when his lecture was delivered and his style was both colloquial and verbose The idiom of course is that of a century ago but his endearing character shines through as he rambled over 40 years of clinical practice It is a small wonder to the translator that he had a huge practice and little time for academic activities!

Because of the prolixity of the original manuscript the translation which follows is very considerably abridged and has been placed under headings not found in the original The sequence of the text is unaltered Relevant passages of Roger s footnotes appear in the translator s Discussion

Clinical researches on the congenital communication between two ventricles due to inocclusion of the ventricular septum
By Henri Roger

Among the cardiac malformations which are compatible with (sometimes long) life the commonest which I have seen is a communication between the two ventricles due to lack of occlusion of the superior ventricular septum

I have seen 12 examples and although a few are cyanosed the others are without cyanosis We shall leave aside those with cyanosis as their auscultatory findings are not always relevant to their anatomical status We are concerned with the simple cases i e interventricular communication *without* cyanosis

This cardiac anomaly has no recognizable symptoms its recognition relies solely on auscultation During the last 40 years I have auscultated thousands of children by virtue of oft repeated examination I have been able with pathological-anatomical correlation to distinguish this cardiac anomaly from others and to establish a distinct clinical entity by its murmur which is the characteristic and pathognomonic sign

Auscultatory findings Over the years I have observed in some of the children in my practice a murmur of remarkable intensity which surprised

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me as it was almost the only sign (apart from a thrill) of a cardiopathy The murmur did not coincide with any other physical signs, nor with functional disturbances indicating a valve lesion or anemia (Anyway chlorotic anemia is not primarily a disease of childhood—murmurs in little children always have an organic origin)

What surprised me equally as much when I followed these children up was that the same murmur was there even after months or years with the same characteristics unchanged and without new physical signs without apparent deterioration in general health and always without cyanosis

Then follows the social history of three patients with the pathognomonic murmur who presented several years apart

These patients who presented far apart from one another were to my observation hard to interpret What I asked myself was this cardiac murmur if not associated with endocarditis However if the murmur depended on abnormality of any of the heart valves why did its intensity and quality not alter as the disease progressed? Furthermore why were the severe functional disturbances of endocarditis not manifest? On the other hand the prolonged innocence of this endocarditis seemed astonishing to me so I asked myself if these children had a congenital circulatory anomaly and did the murmur not indicate the site of an intracardiac communication where the stream passed through the defect Then I thought if this is the case why were they not cyanosed as it is generally agreed that cyanosis always results from intracardiac communication and consequent mixing

Clinico-pathological correlation It was in the dissecting room of the Children s Hospital in about 1861 that enlightenment came to me and I discovered the reason for these obscure and apparently contradictory findings I discovered at the necropsy of a 12 year old boy who had died of a comminuted fracture a congenital cardiac anomaly which consisted of a deficiency of the superior part of the ventricular septum—there was no pulmonary stenosis Neither the skin nor the mucous membranes had been blue in life It goes without saying that the malformation was completely missed in life—nobody had auscultated him An entirely pardonable oversight in a surgical service!

Clinical chance had presented these odd things and anatomic-pathological chance explained them to me The autopsy showed me that intracardiac defects can exist without cyanosis so my observations were made more comprehensible I had no more doubts that my earlier observations indicated the same malformation so fortuitously demonstrated in that cadaver Applying this morbid anatomy finding I immediately concluded that the murmur with the peculiar characteristics which I had heard in my little patients was the pathognomonic sign of the malformation. It explained the findings too of other auscultators in acyanotic children Thus are explained those cases which I was able to follow for a long time—they proved my opinion that a defect of the ventricular septum without pulmonary stenosis is a simple anomaly which compromises neither life nor health The malformations seen clinically are rare and are recognized by mere luck. It is probable because of all the new pathological states being described that we shall discover plenty more now that there is research and accurate observations are being made The following is what happened to me On 30th July last a youth of 17 came to me for a health certificate for him to be a postman He was of small stature but well built and robust in appearance He denied serious illness and had no bronchitis He had neither palpitations nor dyspnea and said he could run as well as his friends. Placing my ear to the precordial region I heard a harsh murmur lasting throughout the cardiac cycle, rather than during any particular event. The murmur had maximal intensity between the nipple and the sternum especially the latter Thence it radiated equally in all directions diminishing by degrees the further away one went It coincided with a tremendous thrill. The vertical dullness did not exceed the recognised line of 1 cm (from the third rib to the fifth interspace) The big cardiac impulse was seen at the sternocostal junction not the apex

If one compares the symptoms of cardiopathy in this young man with those which I have outlined how can one diagnose anything other than a defect of the ventricular septum? Ventricular septal defect is not usually the first thing one thinks about In most cases the diagnosis is made after successive examinations when the observer can assess the true significance of the murmur

Differential diagnosis The diagnostic data are above all provided by auscultation but also by comparison of local and general symptoms and by additional considerations Suppose for exam

ple that one had verified by auscultation a cardiac murmur in a babe in arms One would be hard put to determine its semeiotic value * Is it endocarditis with an organic murmur? Endocarditis primary or secondary (such a splendid cause of abnormal heart sounds) is not a disease of early life and I cannot recall ever having seen it under 2 years of age I published a case of rheumatic endocarditis in a 3 year old and I have recently seen one with cold endocarditis at 33 months Is the murmur functional? But anemia due to many things (rickets tuberculosis and most of all malnutrition) all common in early life does not cause murmurs Murmurs in babies are more often a sign of an anomaly of circulation than a disease

I shall now summarize the physical and especially the stethoscopic signs on which I base my diagnosis of ventricular septal defect I have said that the loudness of the murmur indicating ventricular septal defect had peculiar characteristics It is usually of quite remarkable intensity and heard maximally not at the apex like atrioventricular valve disorders nor at the right base of the heart as in aortic stenosis nor the left base like pulmonary stenosis but in the precordium where the septum is The murmur is unique and prolonged It begins in systole and lasts through the two normal sounds (this never happens in endocarditis) It replaces and usually masks the normal sounds It is fixed and not propagated in the great arteries whereas most pathological murmurs result from stenosis of a valve It is best heard in the midline where its intensity is maximal and is heard equally in all directions It diminishes equally regularly as the ear moves away It coincides with a big cardiac impulse and with a vigorous thrill

Expectation of life The chances of survival with anomalies are positively better than with heart disease I have seen several children recover from acute endocarditis but I have never seen one with chronic disease live to grow up—they cannot look forward to a cure or to more than an average of 10 years of life In (*congenital malformations*) the average is two or three times longer Several of my patients have been followed for periods up to 15 years The children grew up like other children and their general health was not compromised by their cardiac malformation The young girl whose history we cited in our Treaty of Auscultation is now 16 and perfectly well The teenager whom I saw at 17 was perfectly fit to undertake the laborious job of a postman During the last 20 years I have occasionally visited a lady as her medical attendant (I had looked after her children) She had always enjoyed excellent health so you may imagine my amazement when on auscultation I heard a murmur which seemed to me to have the characteristics already described I asked her if any doctor had found anything wrong with her heart and she told me that Guersant Sr (that celebrated pediatrician who was my master in pediatric pathology) had examined her as a baby and diagnosed a congenital anomaly This lady is now over 50 the mother of four and in perfect health I re auscultated her a few months ago and found again in the precordium the same sound as before with all the characteristics of a ventricular septal defect

Preventive treatment One appreciates that there is no direct treatment of this cardiac malformation Pathological cardiac conditions are congenital and are consistent with an arrest of development They are not susceptible to spontaneous improvement nor to medical treatment nor to surgical intervention At present they are untreatable and likely to remain so Hygiene is the means of ameliorating the effects of this circulatory anomaly so that survival is not just to the average age but can exceed it These children need as the vulgar say to be mollycoddled Respiratory disorders aggravate circulatory disease and vice versa As in infancy in childhood every precaution must be taken against bronchopneumonia Anything which increases the heart rate makes it susceptible to secondary hypertrophy and must be shunned The youngest patients in the cot or their mothers arms are by their sedentary existence protected from circulatory disorders the primary cause of hypertrophy In the first years the anomaly remains absolutely latent (except to the auscultator)

In older children violent games especially gymnastics (much beloved by mothers who would like their children to be little athletes) are absolutely contraindicated The same applies to adolescents and when they reach adulthood one should add this advice (so easy to give so hard to follow and most often unheeded) to abstain from excesses of all kinds One must try to make them understand that their health is the price and that long life will be their reward for moderate habits

*Translator's note Semeiotics is that branch of medicine related to the interpretation of symptoms. It was widely used in the eighteenth and nineteenth centuries

As the poet has it, he who would live long avoids excess In a word from the hygiene point of view, it is proper to treat cardiac malformation as if it were an illness

In the old days consultations about organic heart disease always ended with this last prescription avoid strong moral emotions This formula still in use today, seems to me to be both naive and banal Bad luck and an unhappy life happen we do not need to seek them out the more excitable the nervous system is the more excited it will become when disturbed Sick or well man is not master of his emotions nor can he command joy or sorrow Therefore he cannot voluntarily avoid one or the other still less on medical prescription

Drug treatment It is quite useless and may even be harmful to attempt medication in congenital cardiac malformation Its action may be essential in acquired disease but not in congenital disorders What would be the use of *(drug)* treatment to act upon a malformation which one knows to be incurable Take digitalis for example it is an indispensable medicament which doctors (even those who deny its usefulness) would not dream of being without It is incapable of changing a malformation It would need to be a remedy of unlimited strength and while everyone knows that digitalis is invaluable as a temporary measure in the long term its toxicity outweighs its therapeutic action

What shall we say about poultices to the precordium? In the old days it was the classical treatment for organic heart disease Long ago during my internship at the Hotel Dieu I remember the illustrious Recamier (that most worthy and imaginative practitioner whom nothing ever fazed or dismayed) always prescribed four because he used to say that would cover all aspects of the disease Did the disease ever yield? Most doctors were thus deluded and their convictions were often painfully shaken by necropsy findings Once the diagnosis of ventricular septal defect is made rigorous medication is not indicated in fact the diagnosis proscribes it The doctor s provision cannot reach beyond postponement (by means of hygiene) of the influence of the local lesion on the general health He must not torment and exhaust the patient with rigorous medication which is not only irrational but detrimental The final conclusion of this presentation shall be that ancient adage of medicine *primo non nocere (Firstly do no harm)*

Summary

First The ventricular septal defect is a cardiac malformation which never results in cyanosis despite free mixing of venous and arterial streams The malformation is uncomplicated by pulmonary stenosis, and compatible with long life It is failure of completion of the ventricular septum

Second I have demonstrated the clinical picture because it is important to distinguish between it and other malformations It is characterized by the murmur

Third Differential diagnosis will always be easy if the physical signs are accurately compared

Fourth Age is of capital importance in diagnosis Endocarditis can be said never to occur below two years of age and anemia does not produce murmurs in the very young

Fifth In general terms the prognosis is better than in organic heart disease

Sixth Treatment is contraindicated This is advantageous to both doctor and patient

Then followed some discussion Roger was asked why there was no cyanosis He replied that the lesion he had described was not maladie bleue—he continued

The murmur is produced by the passage of blood from left to right for as M Marey has demonstrated the contractile force of the left ventricle is four times that of the right

M Marc See said I accept without question M Roger s thesis of a pathological disorder which has not been explained adequately until today I note that M Roger has only a single autopsy—a child whom he never saw in life and that he has not necropsied any of the other patients which he described This is regrettable—he should have at least one autopsied case

M Pidoux Has he (Roger) ever seen a cure in these patients—I think I have heard of analogous cases who are well today *Roger* replied I do not think a cure is possible the whole point of this presentation is precisely to distinguish this malformation from other sorts

Discussion

Roger excluded some of his patients from the above presentation because of cyanosis It is unclear whether they had the *maladie bleue* later to be called Fallot s Tetralogy or whether they demonstrated the phenomenon which became known as Eisenmenger s complex The former

seems more likely as he reiterated that in the six patients he described none had pulmonary valve stenosis However he clearly recognised that right to left shunting can occur

In a footnote (p 1077 of the text) Roger considered that the murmur was due to blood passing from left to right through the defect Monsieur Marey has found that the force of contraction in the left ventricle is 128 mm Hg while that in the right is only 25 mm Hg * In cases with concomitant hypoplasia of the pulmonary artery the right ventricle tends to hypertrophy while the left atrophies Thus it is possible that the shunt is reversed blood passes through the defect (with a bruit) from right to left

To a contemporary reader Rogers claim to clinico pathological correlation of VSD is rather exaggerated—one serendipitous VSD hardly makes a malady[1] The fact remains however that Roger s observations on patients with the defect which bears his name are valid to this day

Concerning Roger s references to stethoscopy of which he was a pioneer the instrument he used would have been of the monaural type still used today by obstetricians In Furope direct auscultation (with a silk handkerchief between the ear and the patient) was favored until fairly recently[3] and indeed the translator vividly remembers being the subject of direct auscultation by an aged physician when a child in the early 1940 s[†]

The consideration that murmurs in young children were always organic was widely held at that time The low intensity musical murmur described by Still[4] is probably inaudible with either a monaural stethoscope or a 70 year old silk clad ear There is no reason to believe that ejection murmurs were any less common than they are now Roger himself said that he had performed thousands of auscultations on children and it is most unlikely that such a meticulous practitioner would have missed something so common had it been audible to him and his contemporaries

It is unlikely that Roger implied anything other than the sequelae of rheumatic fever by his use of the term endocarditis There is no reason to suppose infective endocarditis was any more common then in children with normal hearts than it is now but rheumatic fever was extremely common

Roger s consideration that VSD resulted from arrested normal development was widely held at that time and perhaps rather surprisingly persists to the present[5] His contemporary Rokitansky[6] postulated that cardiac malformations followed abnormal development and with respect to VSD particularly the study of both affected and normal hearts[8] has supported this latter view

The consideration that drug treatment was of little value is of interest as is Roger s comment on digitalis toxicity The drug was still controversial even after almost a hundred years The tone of Roger s presentation was one of optimism for his patients despite his recognition that no permanently effective treatment was available for either congenital or acquired heart disease Had he been able to visualize the advances in both surgery and medicine which have taken place since 1879 his optimism would have been amply justified

Summary

A new translation of Roger s description of the clinical and anatomical findings in uncomplicated small VSD is presented Reappraisal of Roger s observations in the light of our present understanding confirms that only our attitudes change diseases remain the same

My thanks are due to Mme M Boyden for her assistance with some of the more obscure passages and for her correction of my errors in translation

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* M Marey performed his study in a horse who was quite unmoved by the procedure, and suffered no ill effect

Incidence of mitral valve prolapse in one hundred clinically stable newborn baby girls an echocardiographic study

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Recent reports have indicated that mitral valve prolapse is a common condition[1 3] Although mitral valve prolapse has been observed in infants its prevalence in infancy has not been established[4] This investigation was designed to study the incidence of mitral valve prolapse in 100 clinically stable newborn baby girls

Material and methods

One hundred baby girls whose ages ranged from one to three days comprised the study group The only criteria for selection were the availability of informed consent from the mothers for echocardiograms to be performed on their children and a stable clinical state The subjects were all from the same institution A complete cardiovascular examination was performed on each infant A 3 5 MHz transducer Ekoline 20 ultrasonoscope and a Honeywell 1856 recorder were used The echocardiograms were recorded from the interspace from which the mitral valve could be seen by placement of the transducer perpendicular or nearly perpendicular to the chest wall Care was taken to avoid inferior angulation of the transducer The criteria used for the diagnosis of mitral valve prolapse were those established by Markiewicz and co workers[1] The echocardiograms were independently reviewed by two observers

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Results

Seven babies were observed to have mitral valve prolapse Five had mid systolic prolapse and two babies were noted to have holosystolic prolapse Shaggy echoes on the mitral leaflets were not seen in any of our patients Left ventricular and left atrial size were normal in all subjects The 93 babies without evidence of prolapse had normal echograms except for one baby who had an eccentric aortic valve (eccentricity index = 1 5) which suggested the presence of a bicuspid valve[4] Three of the seven with echocardiographic evidence of mitral prolapse had mid systolic clicks two of whom had systolic murmurs following the click. The four other babies with echo evidence of prolapse had no abnormal auscultatory signs No abnormal auscultatory features were noted in the 93 babies without echographic evidence of prolapse with the exception of one baby who had a holosystolic murmur at the left sternal border which was suggestive of a ventricular septal defect Her echocardiogram did not reveal evidence of left ventricular volume overload the chest x ray was normal and there were no clinical signs of congestive heart failure No skeletal abnormalities were observed in any of our subjects None had cardiac arrhythmias

A representative example of mitral valve prolapse is shown in Fig 1

Discussion

Several studies have indicated that mitral valve prolapse is common in the adult population Markiewicz and associates[1] studied 100 presum

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ably healthy young females and noted that ten subjects had both phonocardiographic and echocardiographic evidence of mitral valve prolapse while 18 others had either phonocardiographic or echocardiographic evidence of mitral prolapse.[1] Procacci and associates observed a lower incidence of mitral valve prolapse. Their study differed from that of Markiewicz and colleagues in that the initial diagnosis of mitral valve prolapse was made by auscultation and echocardiography was performed subsequently so that patients with silent mitral prolapse would have been missed. We observed a seven per cent (three with auscultatory and echocardiographic evidence of prolapse and four with isolated echocardiographic abnormality) incidence of mitral valve prolapse in newborn girls which was less than that noted by Markiewicz and co-workers. This suggests that although mitral prolapse is seen in infancy the condition becomes more manifest in adult life possibly due to progressive myxomatous degeneration of the mitral valve apparatus. Another possible reason for the higher incidence of mitral prolapse in adults is that prolapse due to other etiologies such as trauma, ischemic heart disease, etc. is seen in the adult population.[3] Only three of the seven babies had auscultatory evidence of mitral valve prolapse. Although silent mitral prolapse is known to occur, the proportion of such subjects (four out of seven babies) with no auscultatory signs is higher than that observed in the adult population.[4]

One baby with a cardiac murmur suggestive of a ventricular septal defect had a normal echocardiogram and chest x-ray. A baby with echocardiographic features consistent with a bicuspid aortic valve had no abnormal auscultatory signs. Thus mitral valve prolapse was the most common cardiac abnormality that was detectable in our group of patients. It should be emphasized that we studied only those babies who were clinically stable and it is possible that because of this neonates with more complex congenital cardiac abnormalities were not included in our group.

In conclusion, mitral valve prolapse was the most common cardiac abnormality that was observed in a group of 100 clinically stable newborn baby girls. The classic auscultatory signs were not present in over 50 per cent of subjects. Serial studies on our group of subjects will yield useful information about the natural history of mitral valve prolapse.



Fig. 1. Echocardiogram of mitral valve which shows holosystolic prolapse (*vertical arrow*).

Summary

Clinical and echocardiographic examinations were performed on 100 clinically stable newborn baby girls. Mitral valve prolapse was noted on the echocardiograms of seven babies. Three subjects had systolic clicks, two of whom had systolic murmurs following the click. The four other babies who had echocardiographic evidence of mitral valve prolapse had no abnormal ausculta-

tory signs Of the 93 babies without evidence of mitral prolapse 91 had normal echocardiograms and auscultatory features one was noted to have a murmur consistent with a ventricular septal defect and another had an eccentric aortic valve on the echocardiogram which was suggestive of a bicuspid aortic valve Serial studies on our group of subjects will yield useful information regarding the natural history of mitral valve prolapse

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Atypical pulmonary stenosis radiological features

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The clinical radiologic electrocardiographic and angiocardiographic aspects of certain types of congenital pulmonary stenosis differ greatly from the frequently encountered valvular stenosis with intact ventricular septum The term atypical pulmonary stenosis is used to describe such cases

This congenital defect is usually seen in poly malformative syndromes sometimes familial to such an extent that when confronted with such a syndrome one must systematically look for this association On clinical examination the systolic ejection murmur is lower and more medial than in the usual pulmonary stenosis and the murmur radiates more in the sternal border than upwards and into the back There is no ejection click and the second pulmonary sound is usually dimin ished On plain chest film (Fig 1) there is no or little prominence of the middle segment with no expanding at this level on fluoroscopy The elec trocardiogram shows a high frequency of right superior axis at the limit between the extreme left and extreme right axis deviation. It is a very particular axis which is surprising It perhaps can be interpreted as being in relation to an intraven



Fig 1 Frontal view Plain film (Case 16) No prominence of middle left segment

tricular conduction disorder but the complete criteria of left anterior hemiblock (initial deflec tion in DI and VL) may not always be found It seems more logical to consider this as being related to an abnormality of excitation

Right heart catheterization demonstrates the gradient between the right ventricle and the pulmonary artery which is usually minimum between 19 and 47 mm Hg in most of our cases These stenoses usually requires no surgical correction

Right heart angiography frequently shows a

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Table I

No	Case	Polymalformation	Murmur location (intercostal space)	Chest film flat middle segment	QRS axis	Right heart cath. Pulm grad (mm Hg) AP/VD
1	W A	Noonan	2nd	–	+ 150	45
2	W V		2nd 3rd	+	−90	40
3	L J					100
4	G P		2nd	+	−30	90
5	L C		2nd	+	+ 120	35
6	L D		3rd	–	+ 60	25
7	P P		2nd 3rd	–		
8	P E		2nd 3rd	–	+ 45	30
9	B C		2nd	–	− 180	60
10	G R	Leopard	4th	–	− 90	16
11	P D		2nd	–	− 20	25
12	B M		2nd	–	−150	45
13	L D		4th	–	+ 90	70
14	B P		3rd	+	− 160	75
15	C W		2nd	+	− 170	60
16	P M		3rd	+	+ 180	47
17	C N	Cafe au lait (Watson)			+ 60	90
18	O F		2nd	+	+ 60	14
19	S M		2nd	–	− 150	15
20	D G		3rd	–	+ 80	14
21	S C	others Thoracic deformithy mental retardation	2nd	+	− 90	30
22	P R	Small stature facial dysmorphism mental retardation cryptorchidy pterygium colli hypoacousia thoracic deformity	4th	–	− 90	35
23	S R	Small stature hypertelorism mental retardation epicanthus	3rd	+	+ 80	10
24	L C	Thoracic deformity deafness	2nd	–	+ 90	10
25	W M A	Hypertelorism mental retardation	2nd	+	+ 45	65

very typical pattern The stenosis is not always valvular (Fig 2) but frequently supravalvular close to the valves or valvular and supravalvular at the same time (Fig 3) The valves are dysplastic (Fig 4) thickened rigid and slightly mobile on cineangiography there is not usually a fine and regular dome image but a diaphragm image It is often difficult to diagnose the supravalvar stenosis which is often mild It can be missed in systole and it is visible in diastole (Fig 5 and 6) It is therefore necessary to look carefully to the whole series of films or the cinefilm in order to compare the views in systole and diastole Supravalvular stenosis can also be more easily diagnosed if the dye is injected in the pulmonary artery than in the right ventricle (Figs 7 and 8) Of course the lateral views are the best to make a correct diagnosis

The exploration of the left heart cavities shows a frequent asymmetrical hypertrophic myocardiopathy (Fig 9) The left ventricle is often thickened and bilocular Dyskinesia is evident on cineangiography The echocardiogram shows the septal thickening and the systolic anterior movement of the anterior mitral valve leaflet

We have collected 25 patients with atypical pulmonary stenosis Five were associated with Noonan s syndrome[1] Noonan s syndrome i s Turner phenotype with hypertelorism and a normal masculine karyotype The thoracic deformity is usual with an angle of Louis very marked a prominent thorax and a mammary deviation

Angiocardiogram site of APS	*Valvular dysplasia*	*Associated cardiac lesions*	*Myocardiopathy*	*Familial context*
Valvular	–	Narrow aorta hypertrophic myocardiopathy	+	+
Valvular and supravalvular	–		–	+
Valvular	–	Pulmonary valvular stenosis + ASD	–	+
Valvular and supravalvular	+	ASD	–	–
Valvular and supravalvular	+	–	–	+
Valvular and supravalvular	–	–	+	+
–	–	–	–	+
Valvular	–	ASD	–	+
Valvular	+	ASD	+	–
Valvular and supravalvular	+	Obstructive Myocardiopathy	+	–
Valvular	+		–	+
Valvular	–	Ductus arteriosus	–	–
Valvular	–	Hypertrophic myocardiopathy ASD	+	+
Valvular and supravalvular	+		–	–
Valvular	–	Arterial hypoplasia hypertrophic myocardiopathy	+	+
Valvular	+		–	–
Valvular and supravalvular	+		–	–
Valvular	+		–	–
Supravalvular and valvular	+	ASD HCM	+	–
Valvular	+	–	–	–
Valvular and supravalvular	+		–	–
Supravalvular and valvular	+	Infundibular stenosis	–	–
Valvular	+		–	–
Valvular	–		–	+
Valvular	+	ASD patent ductus arteriosus distal stenosis of pulmonary artery	–	–

There is mental retardation sometimes a small stature and sometimes a pterygium colli a heart disease is found in 80 per cent of cases Eleven cases were associated with genetic cardiac cutaneous syndromes (seven Leopard s syndrome and four Watson s syndrome) The Leopard s syndrome of Gorlin[2] is an association of lentiginosis electrocardiographic conduction abnormalities occular disorders mainly hypertelorism pulmonary stenosis abnormalities of urinary tract mental retardation deafness The Watson s syndrome is the association of café au lait spots and atypical pulmonary stenosis Nine cases were associated with different findings such as craniofacial dysplasia and mental retardation

There is a special prognostic implication which does not arise from the atypical pulmonary stenosis which is mild and fixed but from the hypertrophic myocardiopathy which is progressive In one of our cases the myocardiopathy appeared between two catheterizations Abnormalities of intraventricular conduction are slowly progressive

The grouping of these different syndromes among themselves seems important when studying cardiologic aspects There is probably a pathogenetic peculiarity probably a diffuse malformation syndrome closely related with or similar to phakomatosis

In conclusion atypical pulmonary stenosis is defined as atypical clinical electrocardiographic and radiologic findings when compared with the



Fig 2 Lateral view of right ventriculography (Case 15) Atypical pulmonary stenosis



Fig 3 Lateral view of right ventriculography (Case 10) Valvar and supravalvar pulmonary stenosis



Fig 4 Lateral view of right ventriculography (Case 6 Dysplastic pulmonary valves.



Fig 5 Lateral views of right ventriculography (Case 7) The mild supravalvar stenosis is visible only in diastole and s masked in systole (Case 22)

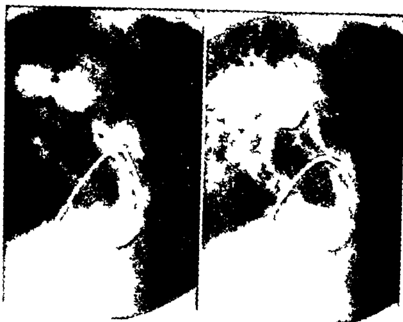


Fig 6 Lateral views of right ventriculography (Case 19) As in Fig 5 the supravalvar stenosis can be diagnosed only in diastole



Fig 7 Lateral views of right angiography (Case 17) The supravalvar stenosis appears at the injection site in the pulmonary artery only



Fig 8 Lateral views of right angiography in the pulmonary artery (Case 13) The supravalvar teno is is visible but could be missed on lateral views in systole *(Fig 6)*



Fig 9 Frontal iews f left ventriculograph (Case 19) Hypertrophic myocardiopathy of the left ventricle

usual pulmonary stenosis It occurs in special circumstances such as familial disorders of the type of Noonan s syndrome as a ca diac cutaneous syndrome or with multiple associated malformations There is a special prognostic implication because of a frequent progressive left myocardiopathy Atypical pulmonary stenosis is probably one symptom of a diffuse malformation syndrome closely related with or similar to phakomatosis

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Use of apexcardiography in the assessment of myocardial function in aortic stenosis

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The evaluation of left ventricular function in patients with aortic stenosis has mainly depended on data derived from left ventricular pressure tracings[1] or cineangiography.[2] Their use, however, is limited by the need for direct heart catheterization, which is an inconvenient, costly, and partially hazardous procedure not suitable for repeated applications. Recently, it has been demonstrated that parameters derived from the left apexcardiogram (ACG) and its first derivative correlate with indexes of myocardial function derived from invasive methods in various cardiac diseases. Accordingly, several amplitude and time criteria of the quantitative apexcardiography have been introduced in the clinical cardiology for the bedside evaluation of cardiac function.

The present study was designed to evaluate the relative importance of various parameters measured externally in the ACG in detecting decreased myocardial function in patients with aortic stenosis. This was investigated using simultaneous high fidelity apex and pressure tracings by comparing first the validity of each of the mentioned noninvasive measures for separating patients with decreased from those with normal ventricular function, and secondly the correlations showing these parameters with widely used indexes of myocardial function derived from invasive methods.

Subjects and methods

Subjects. Left apex tracings were obtained in 176 subjects. All were in sinus rhythm; the QRS did not exceed 0.1 sec in duration.

Normals. The 153 individuals ranged in age from 17 to 59 years (mean age 36 ± 17 [mean ± standard deviation] years), consisting of 90 young (age range 17 to 25 years) and 63 middle aged (34 to 59 years) subjects. No previous history of heart disease was present, and before registration a complete physical examination, 12 lead electrocardiogram, and x-ray were normal.

Patients were divided into two subgroups for the purpose of analysis. Patients with various severity of aortic stenosis who had within normal limits at least two of the three indexes, maximal rate of left ventricular pressure rise (max dP/dt), peak measured velocity of shortening of the contractile elements (V_{pm}), and cineangiographic ejection fraction (EF), comprised Group I, and those having at least two of the mentioned internal indexes of myocardial function below normal comprised Group II, as shown in Table I. In our laboratory[1] the lower limit of normal (i.e., mean normal value minus 2 SD) for max dP/dt is 1350 mm Hg/sec, for V_{pm} 1.14, and for EF 0.60.

Group I. This group comprised 12 patients with slight to severe aortic stenosis. Mean aortic valve gradient (ΔP) was determined by integration of the area between the left ventricular and aortic pressure tracings during the ejection phase of left ventricular contraction and the aortic regurgitation fraction (f.) by the thermodilution meth-

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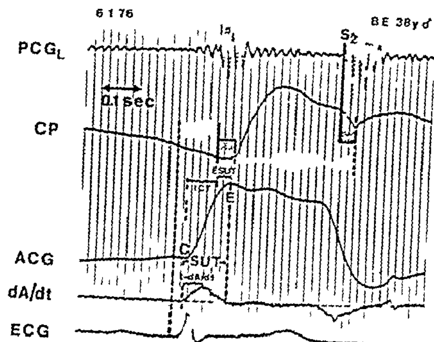


Fig 1 Simultaneous record in a normal subject of a left apexcardiogram *(ACG)* its first derivative *(dA/dt)* carotid pulse *(CP)* external phonocardiogram (PCG_L = low frequencies) and Lead II of electrocardiogram *(ECG)* *C* = the onset of the systolic upstroke of ACG *ESUT* = ejectional systolic upstroke of ACG *ICT* = isovolumic contraction time *SUT* = systolic upstroke time *t-dA/dt* = time to peak dA/dt Paper speed 200 mm per second. The SUT consists of two parts the ICT and the ESUT

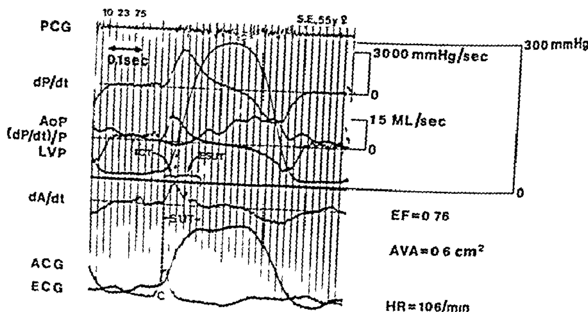


Fig 2 [illegible] ultaneous re[illegible]d [illegible] [illegible]rdi[illegible]gram *(ACG)* and its first derivative *(dA/dt)* left ventricular pressure [illegible] *P)* and it[illegible] first de[illegible] [illegible] [illegible]rt[illegible] pressure *(AoP)* in[illegible]tantaneous quotient *dP/dt* to total pressure [(d[illegible] dt) *P*] extern[illegible] [illegible] [illegible]ram *(PCG)* and Lead II of the electrocardiogram *(ECG)* from a patient with severe aorti[illegible] [illegible] [illegible]ardial functi[illegible]n *AVA* = aortic valve area *EF* = angiographic ejection fracti[illegible]n *HP* = heart [illegible] [illegible] mm per se[illegible]nd Other abbreviations as in *Fig 1* The SUT is within normal limit[illegible] [illegible]

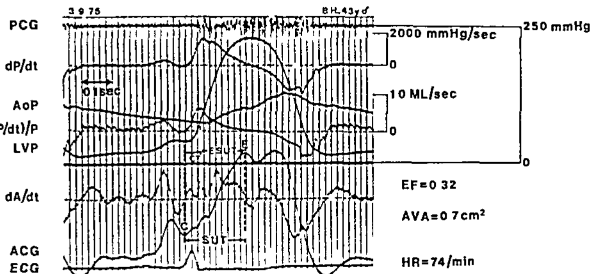


Fig 3 Same variables as described in legend of *Fig 2* in a patient with severe aortic stenosis and depressed myocardial function Note that the SUT is markedly prolonged (201 msec) due to prolongation of the ESUT (146 msec)

od[15, 1] Eight patients had severe ($\Delta P \gtrsim 50$ mm Hg) two a slight ($\Delta P \leq 30$ mm Hg) and one a moderate ($\Delta P = 30$ to 50 mm Hg) aortic stenosis Seven patients of this group had no associated valvular disease whereas four had a slight aortic incompetence (f $\leq$ 0 30) and one a slight mitral incompetence with a mitral regurgitation fraction (f_m) of 0 05 which was estimated by evaluating the combined aortic-mitral regurgitation fraction by thermodilution

Group II consisted of 11 patients with moderate to severe aortic stenosis Ten of them had a severe and one a moderate aortic stenosis (Table I) Further ten of these patients had an accompanying aortic incompetence (f $\leq$ 0 30) and two of them additionally showed a slight mitral incompetence($f_m \leq$ 0 30)

Selective coronary arteriography was carried out at the end of the investigation in all patients and no coronary artery disease was detected Furthermore there were no signs of localized wall motion abnormalities at left ventricular cineangiography

Methods All external and internal tracings of this study were recorded on a 8 or 16 channel Electronics for Medicine oscillograph (DR 8 and DR 16 respectively) at a paper speed of 200 mm per second (Figs 1 to 3)

Apexcardiography All apex tracings were registered at the site of the maximal apical impulse during mild expiratory apnea with the patient in the left recumbent position The recording device is described in our previous studies[1, 13, 17] the pulse transducer had an infinite time constant and no measurable time delay[1] In 49 normals the carotid pulse was recorded simultaneously with the ACG by an identical transducer held by hand at the point of maximal excursion of the carotid pulse In 23 patients with AS the ACG s were obtained during left heart catheterization simultaneously with the internal pressure curves The following measurements were made from the apex tracings

1 Systolic upstroke time (SUT) was measured from the onset (C point) to the end (E point) of the protosystolic upstroke of the ACG (Figs 1 to 3) In the absence of sharp C and/or F points the SUT was measured using the first derivative (dA/dt) of the ACG as the interval from the point where dA/dt ascends from the zero line to the point where it reaches this line again after having reached its maximal peak(s)[1] as demonstrated in Fig 2 in which no sharp E point is present

2 Isovolumic contraction time (ICT) was given in the normals by subtracting the transmission time of the carotid pulse from the interval between the onset of the upstrokes of the apex and carotid pulse tracings[13, 1] as demonstrated in Fig 1 in the catheterized patients from the onset of the apexcardiographic upstroke to the cross over of the pressure curves of the ascending aorta and the left ventricle (Figs 2 and 3)

Table 1 Summary of patient data

Pt no	Age and sex	Diagnosis	HR (/Min)	SUT (msec)	ICT (msec)	ESUT (msec)	t-dA/dt (msec)	A/H (%)	LVSP (mm Hg)
Group I									
1	18M	AS AI	66	124	61	63	—	2	136
2	56M	AS	76	114	77	37	67	7	180
3	49M	AS	57	120	38	82	45	10	170
4	69F	AS	100	96	43	53	43	8	241
5	55F	AS	106	106	33	73	35	11	260
6	46M	AS AI	70	139	29	110	72	11	210
7	20M	AS	74	112	71	41	34	17	146
8	62M	AS AI	87	113	63	50	56	26	270
9	43M	AS AI	74	115	47	68	49	23	267
10	20M	AS	77	140	83	57	60	5	158
11	45M	AS AI	74	121	48	73	—	10	258
12	52M	AS	76	121	65	56	—	13	236
Mean	45		78	118	55	64	51	12	207
±SD	17		14	12	18	20	13	7	54
Group II									
13	67M	AS	49	165	64	101	40	6	218
14	41M	AS AI	67	162	63	99	61	8	179
15	61M	AS AI	68	208	118	90	58	18	196
16	43M	AS AI	74	201	55	146	106	33	227
17	61M	AS AI	107	158	72	86	—	8	207
18	58M	AS AI MI	69	141	38	103	44	17	169
19	58M	AS AI MI	65	157	38	119	40	15	200
20	58M	AS AI	74	143	47	96	60	19	15
21	62M	AS AI	75	142	60	87	66	2	214
22	60M	AS AI	77	153	70	83	63	11	237
23	53M	AS AI	86	144	54	90	45	22	203
Mean	57		73	165	64	101	64	14	200
±SD	8		14	26	8	20	23	9	26
P	< 0 05		NS	<0 001	NS	<0 001	NS	NS	NS

Abbreviations A/H = a wave percentage amplitude to total vertical height of the apexcardiogram AI = aortic incompetence AS = aortic stenosis AVA = aortic valve area CI = cardiac index DAP = diastolic aortic pressure ΔP = pressure gradient across the aortic valve EF = angiographic ejection fraction ESUT = ejectional systolic upstroke time of the apexcardiogram F = female HR = heart rate ICT = isovolumic contraction time LVEDP = left ventricular end-diastolic pressure LVSP = left ventricular systolic pressure M = male max dP/dt = maximal rate of rise of left ventricular pressure MI = mitral incompetence ML = muscle lengths NS = not significant (P > 0 05)—P values were obtained by unpaired Student's t test P = probability SAP = systolic aortic pressure SD = standard deviation t dA/dt = time from onset to peak of the dA/dt of the apexcardiogram V_{pm} = peak measured velocity of shortening of the contractile elements

3 Ejectional systolic upstroke time (ESUT) was determined in the normals by subtracting the ICT from the SUT (Fig 1) and in the catheterized subjects from the cross over of the ascending aorta and left ventricular pressure curves to the end of the SUT (Fig and)

4 Time to peak dA/dt (t-dA/dt) was defined as the interval between the onset to peak of the apexcardiogram to the first derivative dA/dt as shown in Fig could not be measured when multiple peaks were present

5 A wave percentage amplitude (A/H) was calculated as the a wave amplitude (A) in percent of the total vertical height (H) of the ACG

Left heart catheterization and angiography After right heart catheterization a tipmanometer was introduced into the left ventricle either by the retrograde route or following puncture of the septum This manometer had a flat frequency response from 0 to 18 000 Hz and an infinite time constant Cardiac output was determined by the thermodilution method The following measurements were made (Figs 2 and 3) left ventricular systolic pressure (LVSP) left ventricular end-diastolic pressure (LVEDP) systolic aortic pressure (SAP) and diastolic aortic pressure (DAP) From the left ventricular high fidelity pressure tracing the first derivative (dP/dt) was

LVEDP (mm Hg)	*SAP (mm. Hg)*	*DAP (mm Hg)*	*ΔP (mm Hg)*	*AVA (cm)*	*max dP/dt (mm Hg/sec)*	*V_{pm} (ML/sec)*	*CI (L/min/M)*	*EF (–)*
19	113	77	15	2 1	1 09	1.27	5.8	0 68
11	104	78	58	0 7	1551	1 13	3.2	0 69
14	123	75	2[illegible]	2 0	2190	1.36	5 6	0 74
11	96	57	96	0 4	2[illegible]11	1.24	3.5	0 72
19	146	80	81	0 6	2989	1 49	3 0	0 76
22	116	63	70	0 6	1849	1 13	3.3	0 70
17	135	98	6	2 1	18 6	1.50	4 4	0 83
24	140	79	108	0 5	2276	1 43	3 9	0 74
38	143	81	9[illegible]	0 6	2016	0 [illegible]3	4 0	0 67
17	101	77	46	1 0	1736	1 03	4 0	0 66
11	148	9[illegible]	97	0 5	2628	1 47	3.9	0 66
18	144	80	86	0.5	1568	1 01	3.2	0 69
18	1 6	[illegible]8	65	1 0	2046	1.23	4 0	0 71
8	19	11	35	0 [illegible]	437	0 24	0 9	0 05
6	14[illegible]	68	61	0.8	988	0 42	2.6	0.30
23	110	71	51	0 7	1164	0 71	3 6	0 44
14	109	74	64	0 5	1116	0 77	1.9	0 49
40	1[illegible]7	74	83	0 7	1652	0 62	2.9	0.32
19	126	76	74	0.3	130[illegible]	0 68	2 1	0.34
38	111	49	5[illegible]	1 1	867	0 5[illegible]	2.9	0 46
3[illegible]	98	54	78	0 9	1467	0 67	3 4	0 57
41	109	56	43	0 7	1830	0 46	1.9	0.51
17	157	76	58	0 9	[illegible]353	0.94	3.3	0 55
8	136	68	90	0 8	1803	1 06	4 7	0 5[illegible]
33	1[illegible]7	9	6[illegible]	0 8	13[illegible]3	0 66	2 7	0.57
25	1[illegible]3	67	6[illegible]	0.8	1445	0 68	2.9	0 46
13	17	8	15	0.2	436	0 19	0.8	0 10
NS	NS	<0 01	NS	NS	<0 005	<0 001	<0 01	<0 001

obtained by a circuit with a time constant of 0 8 msec The quotient of dP/dt and ventricular pressure (P) i e (dP/dt)/P was determined instantaneously throughout the cardiac cycle by an analog calculating unit with a time constant of 1 1 msec The velocity of shortening of the contractile element during the isovolumic phase of the left ventricular contraction (V_{CE}) was calculated as (dP/dt)/K P in terms of muscle lengths (ML) per second K represents the modulus of elasticity of the series elastic components and amounts to 28 cm Contractility was assessed by the actual value of peak measured velocity of shortening of the contractile elements (V_{pm}) Left ventricular cineangiograms were performed in the right anterior oblique and in the anteroposterior position Contrast dye (Urografin 76 per cent Shering Berlin) was delivered in amounts of 25 to 40 ml by a ECG triggered power injector (Contrac Siemens Zurich) The EF was calculated according to the area-length method of Dodge and associates [8] as well as by the single plane method of Greene and associates The formula for the EF was

$$EF = 1 - \frac{A_s \quad L_D}{A_D \quad L_s}$$

where A_D and A are the end diastolic and end systolic area respectively being determined by planimetry L_D and L_s are the end diastolic and end systolic long ventricular axis respectively being drawn from mitral-aortic junction to the apex

Results

The over all data of the catheterized patients are summarized in Table I Group I comprised patients with normal and Group II those with decreased myocardial performance The indexes

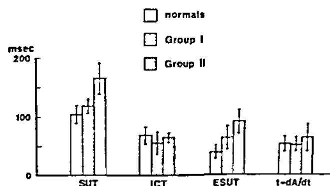


Fig 4 Mean values of temporal apexcardiographic parameters ± 1 standard deviation of normals patients with aortic stenosis of Groups I and II Abbreviations as in *Fig 1*

max dP/dt and EF were within normal limits in Group I whereas the V_{pm} was decreased in five patients (47 per cent) of this group The following measurements showed a significant difference in these two groups the EF and the V_{pm} at $P < 0.001$ the max dP/dt at $P < 0.005$ and the cardiac index as well as the DAP at $P < 0.01$ In contrast the following variables showed no significant difference the resting heart rate (HR) the LVSP the LVEDP the SAP the ΔP and the systolic aortic valve area (AVA)

The systolic upstroke time of the ACG termed SUT was accurately measurable in all subjects using the first derivative of the apex tracing (Figs 1 to 3) Apex tracings from 20 normals who manifested spontaneous changes in sinus rate of 10 to 27 beats/minute (mean 19 beats) during the expiration were analyzed and further linear regression analysis was performed between SUT and HR in order to determine whether there was any rate dependence of the SUT No difference in the SUT was present from cycle to cycle in these subjects However the SUT showed a significant ($P < 0.001$) although only weak inverse correlation with spontaneous heart rate over a range from 42 to 119 beats/minute ($r = 0.46$) a correction for heart rate therefore not being necessary when the heart rate does not differ greatly Further there was no correlation between SUT and age in normals over a range from 17 to 59 years and no significant difference of SUT between females and males

The onset of the apexcardiographic systolic upstroke occurred in all catheterized patients almost simultaneously with the onset of the upstroke of the left ventricular pressure curve the former following the latter by only 3 ± 4 msec (Figs 2 and 3) this being in accordance to our previous findings in controls[1] and in patients with various heart diseases[11-13] The end of the SUT in 20 of the 23 patients (87 per cent) was an easily definable E point and always followed the cross over of the pressure curves of the ascending aorta and the left ventricle in a very variable way as evident from Figs 2 and 3 Thus the SUT consisted of two parts the first is the time between the onset of the systolic upstroke of the ACG and the onset of the ejection phase of the left ventricle which represents the isovolumic contraction time (ICT) and the second that between the onset of the ejection and the summit of the protosystolic upstroke which we termed ejectional systolic upstroke time (ESUT) as shown in Figs 1 to 3

Table II Correlations between apexcardiographic and internal indexes of myocardial function

	LVEDP	*max dP/dt*	V_{pm}	*CI*	*EF*
SUT	(−0.09)	−0.63	−0.69	−0.4[illegible]	−0.85
ICT	−0.43	−0.45	(−0.16)	(−0.21)	(−0.31)
ESUT	+0.42	(−0.38)	−0.67	(−0.38)	−0.[illegible]
t-dA/dt	(−0.02)	(−0.07)	−0.44	(−0.29)	−0.[illegible]
A/H	+0.68	(−0.07)	(−0.23)	(−0.27)	(−0.12)

Abbreviations as in Table I
Values in parentheses = $P > 0.05$
$P < 0.05$
$P < 0.01$
$P < 0.001$

The SUT averaged 104 ± 15 msec in normals As is evident from Table I and Fig 4 the SUT was longer (118 ± 12 msec) in Group I although this difference did not reach a significant P value In contrast the mean value of SUT was markedly prolonged (165 ± 26 msec) in Group II A highly significant difference was also obtained between Groups I and II Linear regression analysis was performed between SUT and internally derived measurements (Table II) There was a strong inverse correlation between SUT and EF ($r = -0.85$ $P < 0.001$) which held over a wide range as demonstrated in Fig 5 Further SUT showed less close negative correlations with V_{pm} ($r = -0.69$) (Fig 5) and with max dP/dt ($r = -0.63$) there was a weak association with the cardiac index In contrast the SUT was not significantly correlated with LVEDP

The first component of SUT namely the ICT averaged in normals in whom apex and carotid pulse tracings were simultaneously recorded

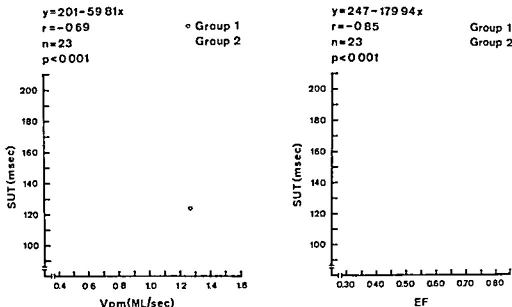


Fig 5 Relationship between systolic upstroke time *(SUT)* of the apexcardiogram and peak measured velocity of shortening of the contractile elements (V_{pm}) *(left panel)* and between SUT and angiographic ejection fraction *(EF)* *(right panel)*

69 ± 15 msec it was within normal limits in both groups (Table I and Fig 4) The ICT was significantly although weakly correlated only with LVEDP and max dP/dt (Table II) The second component of the SUT the ESUT averaged in normals 39 ± 12 msec this being in excellent agreement with our previous findings in catheterized subjects without left heart disease [7] The ESUT was significantly longer in Groups I and II (64 ± 20 msec and 101 ± 20 msec respectively) these mean values being also significantly different (P < 0 001) (Fig 4) This ejection component of the SUT showed furthermore significant (P < 0 001) correlations with EF (r = −0 74) and V_{pm} (r = −0 67) as shown in Fig 6 There was furthermore a positive association between ESUT and LVEDP (r = +0 42) In this context it should be emphasized that neither ESUT nor SUT showed significant correlation with the following variables LVSP SAP DAP ΔP and AVA

The time to peak dA/dt called t dA/dt could not be measured in 52 of the 153 normals (34 per cent) and in four of the 23 patients with aortic stenosis (17 per cent) due to the presence of multiple peaks This time interval in normals averaged 53 ± 13 msec it was within normal limits (51 ± 13 msec) in Group I and slightly statistically not significantly prolonged (64 ± 23 msec) in Group II (Table I and Fig 4) The t dA/dt showed a strong inverse correlation with EF (r = −0 72) it was only weakly correlated with V_{pm} and max dP/dt as evident from Table II

A wave percentage amplitude termed A/H in normals averaged 8 ± 4 per cent it was within normal limits in both groups of patients (Table I and Fig 4) This amplitude parameter was significantly correlated only with the LVEDP (r = +0 68) as evident from Table II All patients with increased A/H (i e over 16 per cent) showed also an increased value for LVEDP (> 12 mm Hg) whereas ten of 15 patients (67 per cent) with normal A/H showed an increased LVEDP (Table I)

Discussion

Quantitative apexcardiography has been shown to be of value in the noninvasive assessment of myocardial function Relative amplitude parameters and time intervals can easily be measured in the apex tracing and its first derivative because calibration is not required In order to compare accurately this non invasive with internally derived indexes of myocardial function the ACG s should be recorded simultaneously with pressure tracings and by using adequate apparatus When they are recorded with devices that have too short a time constant partially differentiated curves are obtained Temporal and ampli

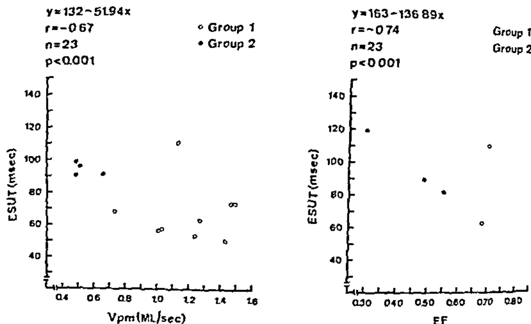


Fig 6 Relationship between ejectional systolic upstroke time *(ESUT)* of the apexcardiogram and peak measured velocity of shortening of the contractile elements (V_{pm}) *(left panel)* and between ESUT and angiographic ejection fraction *(EF) (right panel)*

tude parameters derived from such curves may not be quantitatively comparable with those obtained from tracings recorded with devices having a sufficiently long time constant[1,19] Previous studies from our laboratory have shown that the apexcardiographic systolic upstroke time is a valuable single measure of left ventricular function[1,13]

In the present study the usefulness of different parameters derived from the ACG was investigated for the assessment of myocardial function in patients with aortic stenosis For this purpose and in order to avoid the above mentioned instrumental hazards recordings of ACG and of left ventricular pressure were obtained simultaneously during heart catheterization in 23 patients with pure or predominant aortic stenosis using in both cases similar transducers which are suitable for the recording of high fidelity tracings[13]

As indexes of left ventricular function we have chosen the widely used isovolumic contractile measures max dP dt and V_{pm} as well as the angiographic EF We felt justified in doing so because it has been shown that in chronic left ventricular pressure overload from aortic stenosis a combination of pressure and cineangiographically derived indexes appears to be the most reliable way for indentifying patients with depressed contractile function

The most important findings emerging fro[m] the present study are the validity of the apexca[r]diographic SUT in distinguishing between p[a]tients with normal and those with decreas[ed] myocardial function in aortic stenosis and t[he] relationship of SUT with several accepted inte[r]nal contractile indexes in this specific clinic[al] setting The highest correlation coefficie[nt] (r = −0.86) was observed between SUT and E[F] as is evident from Table II and Fig 5 Less stro[ng] although statistically highly significant were th[e] correlations obtained between SUT and V_{pm} (Fi[g] 5) as well as max dP/dt By contrast the SU[T] did not correlate with LVEDP LVSP SA[P] DAP ΔP and AVA Furthermore the SUT wa[s] markedly prolonged in patients with decrease[d] LV function whereas it was within normal limi[ts] in those with normal left ventricular function a[s] evident from Table I and Fig 4 According to ou[r] present results all patients with values over 14[0] msec for SUT had a decreased ejection fractio[n] (Table I and Fig 5) These observations indicat[e] that in patients with aortic stenosis the SUT i[s] (1) related to widely used internally derive[d] indexes of left ventricular function (2) no[t] influenced from chronic pressure overload or the severity of aortic stenosis and (3) useful in sepa[-] rating patients with decreased from those wi[th] normal myocardial function

Analyzing the mentioned correlations showing SUT with internal indexes and its validity for separating patients with decreased myocardial function we compared the correlations showing each of the two components of the SUT namely the ICT and the ESUT with these internal parameters and their values in the two groups of patients As is evident from Table II the ESUT and the SUT showed similar correlations with EF and V_{pm} whereas ICT was correlated only with max dP/dt Moreover ESUT was significantly longer in the patients with decreased myocardial function whereas ICT was not (Table I) These results are in accordance with our previous findings in patients with aortic incompetence [13] Thus it is evident that in patients with aortic valve disease the ESUT is mainly responsible for the value of SUT as an index of myocardial performance This led us to the reasonable assumption that the ESUT may reflect the early ejection rate the latter being found a more sensitive index of left ventricular performance than indexes based on the entire ejection phase [3] However our present study provides no direct evidence for this hypothesis According to our results the other apexcardiographic parameters namely the t dA/dt and the A/H did not show any importance in separating patients with impaired left myocardial performance However the t dA/dt correlated with EF and the A/H with LVEDP (Table II) It is thus evident that compared to the other apexcardiographic parameters the SUT is both more closely correlated with widely used internal indexes of myocardial function and more sensitive in detecting patients with impaired left ventricular performance

Summary

Twenty three patients with pure or predominant aortic stenosis were studied by simultaneous high fidelity apexcardiographic and left ventricular pressure tracings as well as by cineangiographic measurements Apex tracings were recorded additionally in 153 healthy subjects The systolic upstroke time (SUT) of the apexcardiogram was significantly prolonged in the patients with decreased left ventricular function and separated these patients from those with normal function Furthermore SUT correlated significantly with angiographic ejection fraction as well as with contractile indexes derived from isovolumic pressure measurements i e maximal value of left ventricular pressure rise and peak measured velocity of shortening of the contractile elements Thus the SUT is an indicator of the extent of interpatient differences in left ventricular function

In contrast the time from the onset to the peak of the first derivative (t dA/dt) and the A wave percentage amplitude to total vertical height (A/H) of the apexcardiogram were not sensitive in detecting impaired myocardial function the former being however significantly correlated to the ejection fraction and the latter to the end diastolic pressure of the left ventricle

These data demonstrate the superiority of the SUT as an index of myocardial function over the other apexcardiographic parameters The usefulness of SUT is further enhanced by the simplicity of its measurement and its independence from the extent of chronic pressure overload as well as severity of the aortic stenosis However the validity of SUT for assessing changes in the contractile state of the left ventricle requires further investigation

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Total, phasic and regional myocardial blood flow in aortic stenosis

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The mechanism of angina pectoris in patients with aortic valve disease and aortic stenosis in particular is a subject of great interest It is suspected that these patients may have inadequate coronary flow in the presence of normal coronary arteries Coronary angiographic and flow studies have demonstrated abnormal phasic coronary flow in patients with aortic valve disease[1,2] and in dogs with congenital fibrous ring severe subaortic stenosis[3] Several investigators[4] have measured resting myocardial blood flow per unit mass in aortic stenosis with inert gases and have shown no difference in resting myocardial blood flow in patients with aortic stenosis from a control population In contrast Johnson and colleagues[1] have demonstrated reduced left ventricular myocardial blood flow per unit mass in aortic stenosis In experimental studies with chronic aortic obstruction the coronary flow may be affected by the left ventricular hypertrophy[1] as well as by other compensatory mechanisms such as an expanded subendocardial plexus[1] In addition experimental aortic stenosis has usually been produced by external aortic constriction above the coronary ostium which may cause an increased coronary arterial perfusion pressure proximal to the constriction area The purpose of this investigation was to study total phasic and regional myocardial blood flow during different degrees of acutely induced aortic stenosis in open chested dogs utilizing a model of aortic stenosis that did not cause increased coronary perfusion pressure

Methods

Studies were performed in 16 mongrel dogs weighing 22 9 ± 4 3 kilograms The dogs were anesthetized with sodium pentobarbital 40 mg / Kg intravenously The tracheas were intubated and the dogs were ventilated with room air and oxygen using a Harvard respiratory pump Arterial blood samples were monitored to maintain pH between 7 3 and 7 4 pCO_2 between 35 and 40 mm Hg and pO_2 greater than 90 mm Hg The right femoral artery and vein as well as the right brachial artery were isolated and catheterized A mid sternal thoracotomy was performed and the heart was suspended by a pericardial cradle A cannula for microsphere injections was placed in the left atrial appendage and a solid state high fidelity transducer (Koningsberg) was placed into the left ventricle via a left atrial incision Left *ventricular pressure aortic pressure and Vmax*[12] were determined from the high fidelity left ventricular pressure tracings Aortic pressure was measured with a Statham P 23Db strain gauge in 10 dogs and with a solid state transducer (Koningsberg) in six dogs A Statham (model Sp2201) electromagnetic flow probe (2 to 3 mm) was placed on the proximal portion of the left anterior descending coronary artery A Statham 14 to 18

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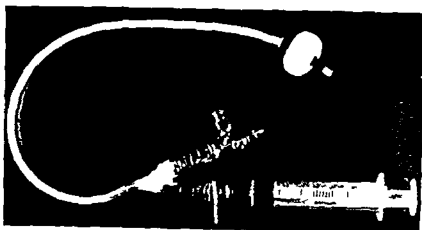


Fig 1A. Catheter tipped balloon for producing aortic stenosis



Fig 1B The balloon is inflated immediately below the level of the aortic valve the catheter tip records the LV pressure

mm electromagnetic flow probe was placed on the ascending aorta approximately 4 cm above the aortic valve Electrocardiogram and pressure signals were recorded on a Brush/Gould Multi Channel recorder as well as on a Hewlett/Packard 3960 FM tape system for later playback and analysis Pressure analysis was hand calculated in addition to a PDP 11/35 computer

The subclavian artery was exposed just above the aortic arch and a catheter specially devised for causing aortic obstruction was advanced to the left ventricle The device used to produce acute temporary aortic stenosis is shown in Fig 1A This type of balloon tipped catheter was made entirely of plastic and contained no metal since metal interferes with the electromagnetic flow field The balloon at the catheter tip had a capacity of 6 c c The amount of aortic obstruction could be varied according to the inflation of this balloon The catheter balloon was advanced across the aortic valve until its tip recorded left ventricular pressures the balloon was then inflated just below the level of the aortic valve (Fig 1*B*) Control observations were made of mean and phasic aortic and anterior descending coronary artery blood flow left ventricular and aortic pressures and of the electrocardiogram. By inflating the balloon just below the level of the aortic valve three degrees of acute aortic stenosis were induced mild moderate and severe (as determined by the peak to peak systolic left ventricular-aortic pressure gradient) Gradients from 1 to 25 mm Hg were considered mild from 26 to 50 mm Hg were moderate and above 50 mm Hg were considered severe stenosis

Coronary blood flow in systole and diastole was determined by a planimetry of corresponding areas of the phasic coronary blood flow A ratio of diastolic coronary blood flow to systolic coronary blood flow was determined as described by Folts and Rowe[14] Zero flow was determined both mechanically and electronically In six dogs a 15 second mechanical occlusion followed by a hyperemic response was used to insure that the coronary flow probe was not occluding the coronary vessel These probes were checked with an in vitro calibration at the end of the experimental series so the measured electromagnetic flow values should be considered relative The absolute flow values for coronary and aortic flow were obtained using the manufacturer s suggested calibration Superimposed pressure recordings from the left ventricle and aorta were used to estimate the ratio of subendocardial coronary flow to the

Table I Hemodynamic variables of 16 dogs with aortic stenosis Mean control values and raw changes from baseline during aortic stenosis

	Control	Aortic stenosis: Mild	Aortic stenosis: Moderate	Aortic stenosis: Severe
Heart rate (beats/min)	151.50 ± 16 57	0 88 ± 9 95	1.32 ± 12 41	0 50 ± 12.36
LV SYS (mm Hg)	116 1 ± 14 9	0 08 ± 11 63	21 71 ± 16 51	56 00 ± 19 43
LV DIAS (mm Hg)	3 9 ± 2 0	0 19 ± 2 66	0 36 ± 3 00	1 60 ± 4.58
Aortic SYS (mm Hg)	118.2 ± 15.95	−15.38 ± 9 05	−16 00 ± 19 06	−17 60 ± 16.30
Aortic DIAS (mm Hg)	85 9 ± 14 1	−10 00 ± 7 13	−9.25 ± 15 11	−16.10 ± 8 60
Ejection time (msec.)	143 62 ± 2? 67	21 6_ ± 12 00	31 85 ± 17.86	37 78 ± 21 76
DPTI (mm. Hg × sec /min)	3 90 ± 0 73	−0 61 ± 0.36	−0.85 ± 0 66	−1 07 ± 1 02
SPTI (mm Hg × sec /min)	3 48 ± 0 70	0.21 ± 0 19	0 61 ± 0 57	1 45 ± 0 70
DPTI/SPTI	1 14 ± 0 19	−0 25 ± 0 12	−0.38 ± 0 11	−0 62 ± 0.27
Vmax (28.8 × length/sec)	71 0 ± 9.94	−1.85 ± 8 77	−1 74 ± 10.29	1.53 ± 10 63
DIAS/SYS ratio	3 46 ± 0 71	0.27 ± 2 92	0 30 ± 2.27	0.26 ± 2.50
Aortic flow (L./min)	2 14 ± 0 91	−0.27 ± 0.36	−0 06 ± 0.55	0 02 ± 0 92
LAD flow (mL/min)	25 4 ± 12.2_	−0.92 ± 8 72	0 71 ± 6 76	3 49 ± 6 3_
DIAS LAD flow (mL/min)	19.5 ± 9 00	−2 61 ± 6.31	−2 08 ± 7 12	−0 66 ± 9.80
SYS LAD flow (ml /min)	6 6 ± 3 98	1.88 ± 5 85	2.38 ± 5 75	3 06 ± 5.22
Endocardium (ml /100g /min)	87 7 ± 22 77	2 69 ± 9 98	7 88 ± 27 65	25 8? ± 29 16
Epicardium (ml /100g /min)	77 6 ± 22 99	0.23 ± 10.32	6.82 ± 23 60	33 71 ± 25 08
Total MYO flow (mL/100g./min.)	83.3 ± 2_ 13	1 76 ± 9 46	8 78 ± 25 11	32.28 ± 27 02
ENDO/EPI ratio	1 18 ± 0 18	0 01 ± 0 10	−0 02 ± 0 08	−0 13 ± 0.21

Denotes s gn ficant change from baseline state ($p < 0.05$)

Abbreviations LV SYS = left ventricular systolic pressure LV DIAS = left ve tricular d astol c pressure Vmax = contractil element velocity at z ro l ad DPTI = diastolic pressure time index ENDO/EPI ratio = ratio f endo ardial coronary blood flow to ep cardial coronary blood flow DIAS/SYS ratio = ratio of diastolic coronary blood flow to ystol coronary blood flow LAD = left anterior descending coronary artery SPTI = systolic pressure tim index

left ventricular oxygen requirements as previously reported by Buckberg and co workers [15] According to this method potential subendocardial perfusion is estimated by using a diastolic pressure time index (DPTI) obtained by planimetry of the area between the superimposed aortic and left ventricular pressure curves in diastole Myocardial oxygen requirements are estimated from a modified tension-time index obtained by planimetry of the area beneath the left ventricular pressure curve from the onset of ventricular systole to closure of the aortic valve Since this is a pressure measurement rather than a tension measurement it is termed the systolic pressure time index (SPTI) The ratio DPTI/SPTI is commonly used as an estimate of the adequacy of the left ventricular subendocardial blood flow

Four differently labeled microspheres were injected into the left atrium in the control situation and five minutes after establishment of mild moderate and severe stenosis Animals were allowed to return to baseline hemodynamic conditions between each degree of aortic stenosis

Myocardial perfusion using techniques reported from this laboratory [6] was measured with 7 to 9 μ microspheres labeled with ^{85}Sr ^{141}Ce ^{51}Cr ^{46}Sc and ^{95}Nb For each flow measurement between 1 35 × 10^6 to 2 81 × 10 microspheres were suspended in 0 13 to 2 2 ml of saline and injected into the left atrium Prior to the injection the vial containing the microspheres and one drop of Tween 80 was vigorously agitated mechanically for at least four minutes Microscopic examination of microspheres dispersed in the manner described above showed that in excess of 98 per cent of the spheres were completely dispersed Occasionally small groups of three to five spheres were observed Starting 30 seconds before injection and continuing until three minutes after injection blood was withdrawn simultaneously from the right brachial and right femoral arteries at 2 06 ml per minute with a Harvard pump

Following the study the animals were killed with an injection of potassium chloride The position of the balloon catheter in relation to the aortic valve leaflets was verified by opening the aorta 3 cm above the valve The heart was

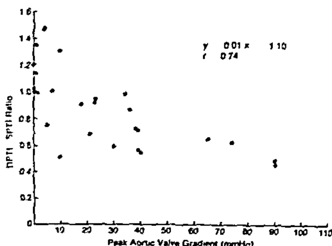


Fig 2 Plot of the DPTI/SPTI ratio versus peak pressure gradient A significant correlation is observed

excised, and the free walls of the right atrium right ventricle left atrium great vessels valves surface vessels and epicardial fat were removed Utilizing the posterior descending coronary artery as a starting point the left ventricle was divided into four equal levels of eight segments each each segment was divided into three layers endocardium mid wall and epicardium of approximately equal thickness Thus the left ventricle was divided into 96 segments and the relative geometric position of each segment was constant from animal to animal Subsequently the myocardial segments were weighed (to the nearest mg) placed in glass tubes and counted for five minutes each in three inch well type sodium iodide gamma counter The average weight of the segments was 0 87 ± SD 0 18 gm

The reference blood samples were divided into aliquots so that their counting geometry was similar to that of the myocardial samples Energy windows utilized were ' Sc 700 to 1500 keV Sr 400 to 600 keV Cr 270 to 370 keV ' Ce 126 to 175 keV and Nb 325 to 400 keV Isotope separation was performed utilizing standard tech niques

The myocardial blood flow was calculated using the following formula MBF = Cm × 100 × RBF ÷ CR where MBF = myocardial blood flow in c c 100 gms per minute CM = counts per gram of myocardium RBF = reference blood flow (rate of withdrawal fr m [illegible]rence arteries) and CR = total counts in [illegible] reference blood The counts in the femor [illegible] d bra hial blood samples were averaged [illegible] mber of spheres present in the brachial [illegible] er oral r ference samples was rarely identical The average di[illegible] ence between simultaneous reference samples [illegible] 4.87 ± 3 73 per cent (mean ± SD) Twenty [illegible] dogs survived the initial surgery Of these [illegible] dogs were deleted because of significant ao[illegible] regurgitation as indicated by the aortic f[illegible] tracings One dog was deleted because of exces[illegible] drop in systolic arterial pressure (< 60 mm H[illegible] One dog was deleted because of abnormal cont[illegible] coronary flow ratio (D/S greater than 5.5) T[illegible] other dogs were deleted because of greater than [illegible] per cent difference between all pairs of refere[illegible] samples this also required deletion of three f[illegible] determinations in the 16 dogs whose data w[illegible] used in the study

The counts per minute sample weight a[illegible] geometric reference number for each segme[illegible] were punched on computer paper tape Sub[illegible] quent analysis was performed with a PDP 11/[illegible] computer Standard statistical techniques [illegible] tests) were utilized to analyze the data. [illegible] results are expressed as the mean ± 1 standa[illegible] deviation

Results

Table I shows a summary of the mean contr[illegible] value and raw changes of measured paramete[illegible] during the induction of aortic stenosis There a[illegible] no significant changes in heart rate for all degre[illegible] of aortic stenosis Vmax was used as a contracti[illegible] ity index and did not change As expected the le[illegible] ventricular systolic pressure increased and th[illegible] aortic systolic pressure decreased proportionatel[illegible] to the degree of aortic stenosis Aortic diastol[illegible] pressure also fell in proportion to the severity o[illegible] aortic stenosis The left ventricular end-diastoli[illegible] pressure did not change significantly from contr[illegible] values during all degrees of aortic stenosis Th[illegible] left ventricular ejection time increased signifi[illegible] cantly with all degrees of aortic stenosis There were significant decreases in the DPTI/SPTI ratio for all degrees of aortic stenosis due to the concomitant decrease in DPTI while the SPTI increased The aortic flow fell slightly during mild aortic stenosis but did not change significantly during moderate or severe aortic stenosis the endocardial flow ENDO/EPI ratio and DIAS SYS coronary flow ratio did not change signifi cantly There was a significant increase in epica[illegible] dial flow during severe aortic stenosis

Fig 2 is a plot of the DPTI/SPTI ratio vs the peak left ventricular aortic pressure gradient. The

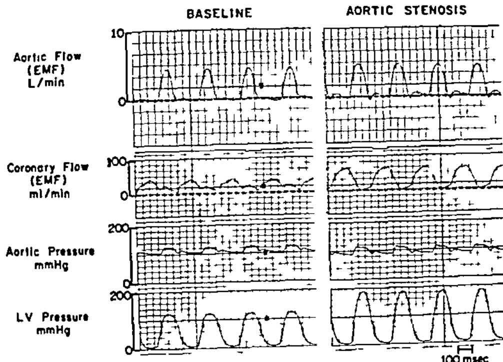


Fig 3 Phasic aortic and coronary blood flows during baseline condition and after induction of severe aortic stenosis. There is no significant change in the aortic flow The phasic coronary flow is still predominantly diastolic during severe aortic stenosis.

correlation coefficient is R = 0 74 indicating a significant relationship between these parameters

The phasic coronary blood flow was predominantly diastolic during the control state and during all degrees of aortic stenosis Fig 3 demonstrates phasic aortic and coronary blood flow during control conditions (DIAS/SYS ratio = 2 45) and after the induction of severe aortic stenosis (peak gradient = 80 mm Hg) it can be appreciated that most of the flow is still diastolic (DIAS/SYS ratio = 4 49)

Fig 4 is a plot of the DIAS/SYS coronary blood flow vs the peak aortic valve gradient There is random distribution and poor correlation (r = 0 07)

Fig 5 is a plot of the total coronary blood flow vs the peak aortic valve gradient There appears to be random distribution and statistical analysis shows no direct correlation (r = 0 32)

Fig 6 is a plot of the ENDO/EPI coronary blood flow ratio vs the peak aortic valve gradient It can be seen that the ratio remains in the same range for all degrees of gradient With severe aortic stenosis however there is only a mild decrease in the ratio due to a greater increase in the epicardial flow than in the endocardial flow

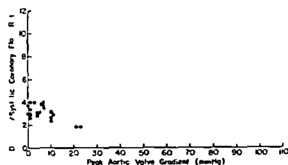


Fig 4 Plot of diastolic/systolic coronary flow ratio versus peak aortic valve gradient There is random distribution.

This decrease in the ENDO/EPI ratio however was not statistically significant Over all there is no correlation between the severity of aortic stenosis and the ENDO/EPI ratio (r = 0 33)

Fig 7 is a plot of a phasic coronary blood flow vs the ENDO/EPI flow ratio There is no direct correlation between these parameters

Fig 8 is a plot of the DPTI/SPTI ratio vs the ENDO/EPI ratio Once again there is no direct correlation between these parameters (r = 0.24)

Discussion

The significant findings in this investigation are the following First in acute experimental steno

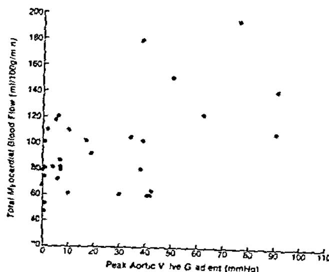


Fig 5 Plot of total myocardial blood flow versus peak aortic valve gradient showing random distribution.

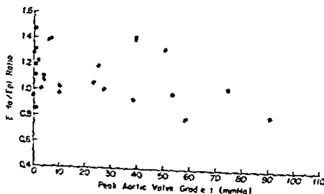


Fig 6 Plot of ENDO/EPI ratio versus peak pressure gradient Only a weak correlation is demonstrated.

sis there are no significant changes in the endocardial coronary blood flow and the ENDO/EPI myocardial flow ratio as determined by the microsphere technique The total coronary flow is however slightly increased during severe aortic stenosis Second the phasic coronary flow is not significantly altered Third the DPTI/SPTI ratio previously considered an estimate of the adequacy of subendocardial flow is significantly decreased and did not reflect the subendocardial flow in the experimental model that we utilized

The endocardial flow or the ENDO/EPI ratio did not change significantly In this report our observations contrast with previous reports on experimental aortic stenosis which demonstrated significant fall in endocardial flow ENDO/EPI ratio as well as in the diastolic/systolic coronary flow It should be noted however that in these previous investigation while proximal supravalvular aortic constriction was prone to induce the myocardial blood flow changes distal aortic constriction did not cause these changes Two factors may have been responsible for the differences between the results and previous investigations[15] It appears that a critical factor was a marked elevation of left ventricular filling pressures (mean left atrial pressure of 30 mm Hg) in proximal aortic constriction[15] Thus, it is likely that the marked elevation of the diastolic pressures in the left ventricular cavity exerted increasing tension on the subendocardial capillaries with consequent decreased endocardial flow In our experiment (during which the LV filling pressures did not increase significantly) the results are more similar to distal aortic constriction and unlike proximal aortic constriction Another difference between Buckberg and colleagues experimental model and our model could also be responsible for some of the differences in results In their model, for instance there was marked increase in systolic

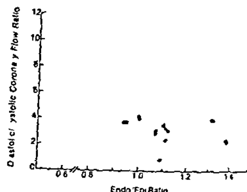


Fig 7 Plot of coronary flow ratio versus ENDO/EPI ratio No correlation is seen between these parameters

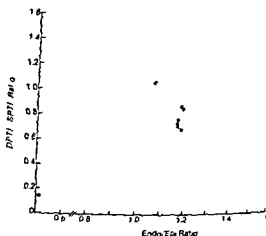


Fig 8 Plot of DPTI/SPTI ratio versus ENDO/EPI ratio Random distribution is observed

aortic pressure and lesser increase in diastolic aortic pressures which may have been responsible for redistribution of coronary flow with systolic component (epicardial flow) becoming greater than the diastolic (endocardial flow)

In regard to the DPTI/SPTI index it is interesting to note that even during severe aortic stenosis when all DPTI/SPTI ratios were less than 0 7 a level at which the endocardial flow would have been expected to be low according to Buckberg and co workers [15] we found a normal endocardial flow and ENDO/EPI ratio Why the DPTI/SPTI did not reflect the endocardial flow or the ENDO/EPI ratio in our experiment may be because this index is also partially dependent on the arterial blood oxygen content which we did not measure routinely in our experiments Other factors that affect the myocardial oxygen demand not reflected in the index are the myocardial contractility and the heart rate but these variables did not change in our animals Later studies by Buckberg and associates[19] have suggested that a DPTI/SPTI of less than 0 5 indicates subendocardial ischemia In a recent study of patients with aortic stenosis and normal coronary arteriogram [8] 33 per cent of 24 patients without angina had a DPTI/SPTI of less than 0 5 indicating less specificity of this ratio than initially indicated In addition another recent study [9] shows no relationship between DPTI/SPTI ratio and values for myocardial blood per beat in a group of patients with aortic stenosis

Data on the regional subendocardial metabolism would be important in interpreting the significance of changes of the DPTI/SPTI diastolic/systolic flow ratio or of ENDO/EPI ratios Unfortunately in humans it is frequently impossible to obtain regional subendocardial metabolic studies In recent studies by Griggs and co workers [2] constricting the aorta proximally to the orifice of the left coronary in experimental acute aortic stenosis failed to show any evidence of anaerobic metabolism in the subendocardium in the resting state

Pyruvate lactate and lactate/pyruvate ratio as well as subendocardial ATP were unchanged in aortic stenosis (mean pressure gradient = 42 mm Hg) when compared to control Only when isoproterenol was administered after creation of aortic stenosis did evidence of anaerobic metabolism develop Thus our findings of normal resting subendocardial coronary flows are in keeping with the results of Griggs and associates [1] It is noteworthy that in their experiments in aortic stenosis the left ventricular filling pressures did not change significantly either again suggesting that the left ventricular diastolic pressure may have a critical effect on the subendocardial flow

Extrapolation of our findings in acutely induced aortic stenosis to patients with chronic long standing aortic stenosis may not be warranted because the latter have elevated left ventricular filling pressures left ventricular hypertrophy and scattered areas of fibrosis—all of which will influence the measurements of epicardial and endocardial flow Nonetheless our findings suggest that secondary circulatory adjustments to the aortic stenosis such as increased left ventricular diastolic pressure in addition to the mechanical factor of the stenosis per se may be important in the distribution of myocardial flow and perhaps in the production of the symptoms of angina pectoris in patients with aortic stenosis

Summary

The effect of aortic stenosis on total phasic and regional myocardial flow was studied in 16 anesthetized open chested dogs An adjustable catheter device was used to produce increasing aortic obstruction the severity of which was judged from the left ventricular aortic peak systolic gradient as mild (< 25 mm Hg) moderate (26 to 50 mm Hg) and severe (> 50 mm Hg) The supply/demand index was estimated from the ratio of diastolic pressure time index to systolic pressure time index (DPTI/SPTI) The ratio of diastolic to systolic coronary blood flow (DIAS/SYS) was determined from the flow tracings Total myocardial flow and endocardial/epicardial flow ratios (ENDO/EPI) were determined by injecting four differently labeled 7 to 9 micron microspheres in the left atrium during control mild moderate and severe aortic stenosis

The supply/demand (DPTI/SPTI) index decreased significantly at all levels of aortic stenosis because of a decrease in DPTI and an increase in SPTI The DIAS/SYS coronary flow ratio and the ENDO/EPI myocardial flow ratio were not significantly changed during aortic stenosis The total myocardial flow was significantly higher than control only during severe aortic stenosis

The results indicate that for all degrees of experimental aortic stenosis there were significant decreases in DPTI/SPTI but no significant changes in DIAS/SYS coronary flow ratio or the distribution of myocardial perfusion Thus in acute, experimental aortic stenosis there is evidence of increased myocardial oxygen demand but endocardial perfusion is not changed significantly

The catheter balloon device was made by Jim Rogers of Jim s Instrument Manufacturing Inc 1208 Highland Court Iowa City Iowa

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Electrophysiological effects of disopyramide phosphate during experimental myocardial ischemia*

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Disopyramide phosphate is a newly released antiarrhythmic agent that has been shown to be useful in various types of rhythm disorders Several studies[1] have documented its efficacy in *suppressing arrhythmias of ventricular origin* either due to digitalis intoxication or coronary occlusion However only scant information is presently available on its effect on ventricular muscle[5] particularly in the presence of ischemia This type of study is needed since the mechanisms of action of disopyramide were determined in normal tissues[1] and the findings extrapolated to the ischemic state

This investigation was therefore undertaken to examine the electrophysiologic effects of this drug on ventricular muscle during myocardial ischemia and to determine whether it exerts differential effects in nonischemic and ischemic myocardium

Methods

Seventeen mongrel dogs weighing 16 to 25 kilograms were anesthetized with intravenous pentobarbital 30 mg/Kg intubated and mechanically respirated with a Harvard respirator The left femoral vein was catheterized for administration of drugs and to obtain blood samples for determination of disopyramide plasma levels The aortic pressure was monitored via a catheter introduced in the left femoral artery using a Statham P23Db transducer The heart was *exposed through a midline thoracotomy and* supported in a pericardial cradle Heart rates were kept constant by right atrial pacing at cycle lengths ranging from 450 to 500 msec after the sinus node was destroyed with an injection of formaldehyde Fine Teflon coated stainless steel bipolar plunge electrodes (0 003 inch diameter) were inserted into the left ventricular myocardium in potentially ischemic and nonischemic zones using techniques previously described[11] The electrodes comprising each pair were placed 1 mm apart In each zone the pair of recording electrodes was placed at a distance of 5 mm from the pair of stimulating electrodes Bipolar electrograms (frequency response 50 to 500 Hz) standard ECG leads and aortic pressure were simultaneously recorded using a Honeywell 1508B Visicorder at paper speeds of 100 to 200 mm/sec

Refractory periods of ventricular myocardium were determined by the introduction of premature stimuli of twice diastolic threshold and 2 msec duration delivered every tenth paced beat Intramyocardial conduction times were determined by measuring the interval from the initial deflection of the QRS in the peripheral ECG to the onset of the major deflection of the local electrograms in the nonischemic and ischemia areas[13]

Disopyramide phosphate (Norpace G D Searle Laboratories) was given intravenously as a

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Table I Changes in refractory periods following ischemia and disopyramide administration

		Control	Post occlusion	Post disopyramide	
				5 15 min	15-30 min.
A	Nonischemic area	285 4 ± 7 8	287 5 ± 9 3	312 6 ± 5 1	30[illegible]2 ± 7 7‡
	Ischemic area	280 9 ± 9 5	254 0 ± 11 2†	298 2 ± 10 3	288 3 ± 13 6‡
B	Nonischemic area	277 0 ± 6 5	280 9 ± 6 3	318 1 ± 8 9	310 5 ± 11.3
	Ischemic area	281 0 ± 6 0	257 8 ± 7 0†	319 7 ± 8 9	29[illegible].8 ± 12.3

In this and other tables values are expressed as mean ± SEM (in msec)
†p < 01 from control.
‡p < 05 from post occlusion
p < 01 from post occlusion
p < 001 from post occlusion.

Table II Changes in intramyocardial conduction following ischemia and disopyramide administration

		Control	Post occlusion	Post disopyramide	
				5 15 min	15-30 min.
A	Nonischemic area	33 0 ± 5 4	34 2 ± 5 9	36 0 ± 6 4	35 0 ± 5 9
	Ischemic area	19 6 ± 3 9	29 9 ± 5 3†	39 6 ± 7 2	38 [illegible] ± [illegible]
B	Nonischemic area	14 3 ± 2 4	14 7 ± 2.3	16 0 ± 2 5‡	14 8 ± [illegible]4
	Ischemic area	22 4 ± 4 1	27 1 ± 4 8†	35 1 ± 6 0 *	33 1 ± 5 7

†p < 01 from control.
‡p < 05 from post occlusion
p < 01 from post occlusion.
p < 001 from post-occlusion.

Table III Changes in intramyocardial conduction following ischemia and disopyramide administration

	Control	Post occlusion	Post disopyramide	
			5 15 min	15-30 min.
Nonischemic area	24 7 ± 5 6	25 5 ± 5 9	27 6 ± 6 2†	26 0 ± 6 1
Ischemic area	20 6 + 2 8	29 0 ± 3 8	38 1 ± 5 1	37.5 ± 5.5

p < 005 from control
†p < .01 from post occlusion
p < 001 f om po t occlusion

3 mg /Kg bolus and two protocols followed In eight dogs (Group A) after obtaining control refractory periods and conduction times in both the nonischemic and potentially ischemic areas myocardial ischemia was produced by ligation of the left anterior descending coronary artery and repeat measurements were obtained 15 minutes later Disopyramide was then administered and values were recorded at 5 and 15 minutes In another series of experiments in nine dogs (Group B) the coronary artery was occluded and similar measurements were recorded after 15 minutes The ligation was then released and the heart was allowed to recover for one hour[13] at which time all measured parameters had returned to control values Disopyramide was administered prior to reocclusion data were recorded 15 and 30 minutes later and were compared to that obtained during the control ligations

Serum disopyramide phosphate levels were determined fluorometrically by G D Searle Laboratories from blood samples obtained before each set of measurements was undertaken

The data obtained from the two protocols were analyzed independently In addition because results were similar data from both protocols

were also grouped together for statistical analysis Statistical significance was determined by using the t test for paired data

Results

Following ligation of the left anterior descending coronary artery the ischemic area showed rapid development of cyanosis and paradoxical motion Within a few minutes ventricular ectopic beats occurred and reached maximal frequency between 5 and 15 minutes After the administration of disopyramide the number of ventricular ectopic beats per minute decreased from 13 ± 5 (mean ± SEM) to 5 ± 3 ($p < 01$) The mean serum disopyramide levels were 3 2 ± 0 7 μg/ml after 5 to 15 minutes of administration and declined to 2 9 ± 0 9 μg/ml after 30 minutes Although in this study we did not attempt to achieve a steady state drug concentration the disopyramide levels were within the therapeutic values of 2 to 4 μg/ml throughout the experiments

The effects of disopyramide phosphate on refractory periods are shown in Table I Group A indicates the experiments where the drug was administered while the coronary occlusion was maintained Group B refers to the experiments where disopyramide was administered prior to reocclusion The grouped data from the both protocols is shown in Fig 1 During control conditions refractory periods in the nonischemic and potentially ischemic areas were similar 280 msec Following coronary ligation refractory periods in the nonischemic areas remained essentially unchanged 284 msec while in the ischemic areas they decreased by 24 msec to 256 msec ($p < 01$) causing a mean disparity of 28 msec in the refractory periods (Fig 1) Five to 15 minutes after disopyramide administration refractory periods lengthened in both the nonischemic and the ischemic areas to 314 msec in the nonischemic areas ($p < 001$) and to 309 msec in the ischemic areas ($p < 001$) The different magnitude of these changes was such that the mean disparity of refractoriness decreased from 28 to 5 msec ($p < 001$) (Fig 1) A similar effect on refractory periods persisted 15 to 30 minutes after disopyramide administration with a prolongation of refractory periods in the nonischemic areas to 306 msec ($p < 01$) and to 291 msec ($p < 01$) in the ischemic areas and thereby a continued

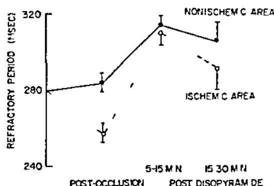


Fig 1 Refractory periods during control state after coronary occlusion and following disopyramide phosphate Coronary occlusion resulted in a disparity of refractory periods of 28 msec that was decreased to 5 msec ($p < 0 001$) after 5 to 15 minutes and to 15 msec ($p < 0 01$) after 15 to 30 minutes of disopyramide administration Values are means ± SEM

decrease in the mean disparity of refractoriness to 15 msec ($p < 01$)

The effects of disopyramide phosphate on intramyocardial conduction times are shown in Table II Again Group A refers to those experiments where the drug was administered while maintaining coronary ligation and Group B to those where disopyramide was given prior to reocclusion Pooled data are summarized in Table III Control conduction times from the onset of the QRS to the electrograms in nonischemic and potentially ischemic zones were similar (Table III) Following coronary occlusion conduction times to the nonischemic areas remained unchanged while in the ischemic areas they prolonged 8 4 msec ($p < 005$) After 5 to 15 minutes of disopyramide administration conduction times were prolonged transiently by 2 msec in the nonischemic zones while in the ischemic zones conduction times were further prolonged by 9 msec ($p < 001$) and remained significantly prolonged at 15 to 30 minutes of drug administration ($p < 001$)

Discussion

In previous studies[1] in intact animals and man it was demonstrated that disopyramide phosphate exerted a significant antiarrhythmic action against experimental and clinical arrhythmias of ventricular origin particularly in the presence of myocardial ischemia [15] In the present study we have shown that disopyramide phosphate had a suppressant effect on ventricular beats during

acute myocardial ischemia at a time when serum levels were within the therapeutic range of 2 to 4 μg/ml[16]

This report indicates that while disopyramide phosphate exerted its antiarrhythmic effect it induced electrophysiological changes in the nonischemic and ischemic areas of ventricular muscle Refractory periods were significantly prolonged in both nonischemic and ischemic myocardium The extent of this effect was such that relative changes in the ischemic areas were of greater magnitude than those in the nonischemic areas and decreased significantly the differences in refractoriness between the two areas A disparity between the two areas of 28 msec was induced by coronary occlusion and significantly reduced by disopyramide phosphate to 5 msec after 5 to 15 minutes and to 15 msec after 15 to 10 minutes of drug administration (see Fig 1) In addition disopyramide slowed intramyocardial conduction in the ischemic areas for at least 30 minutes while having a minimal and transitory effect at 15 minutes in the nonischemic areas

It has been postulated that ventricular arrhythmias are due to disturbances in automaticity conduction or both[17] However it was previously shown[18, 5] that ventricular arrhythmias occurring during the early stages of acute myocardial ischemia are probably due to reentry since automaticity was not found to be increased at the time One of the postulates for these early reentrant rhythms is the nonuniformity of duration of action potentials and refractory periods present in the ischemic ventricle thereby inducing boundary currents[20] It would appear that any drug effect that slows conduction possibly to the point of block and decreases the disparity in refractory periods could make reentrant arrhythmias less likely by converting areas of unidirectional block into bidirectional block

Several in vitro studies [7] of disopyramide phosphate have shown that its electrophysiological effects closely resemble those of procainamide and quinidine These agents decrease action potential amplitude and upstroke velocity prolong the effective refractory period and depress automaticity in normal tissue Kus and Sasyniuk[5] in in vitro studies showed that disopyramide phosphate has differential effects at various sites of the ventricular conduction system with the net result of a decrease in the nonuniform repolarization of these sites Danilo and co workers[?] found that the depressant effects of disopyramide were accentuated as the potassium concentration was increased This finding suggests that the effects of disopyramide and other antiarrhythmic drugs will be more prominent at higher potassium levels[23] The elevated extracellular potassium levels[24] caused by potassium leakage due to membrance disruption in ischemic areas could thus potentiate the drug effects in those areas as seen in our study

Previously, we[5, 26] and others[13, 27] have examined the electrophysiological effects of several antiarrhythmic drugs during acute myocardial ischemia It appears that in addition to several common electrophysiologic effects these drugs share another characteristic namely the differential effects exerted on ischemic areas The bases for the variability in responses are not known but probably are multifactorial Although nonuniform drug *distribution* in the various areas of ventricular myocardium is an important consideration scant information is presently available Preliminary data on propranolol obtained in our laboratory[28] from a protocol similar to that of Group A dogs indicates that substantial amounts of propranolol were present in the ischemic areas following acute coronary ligations The delivery of disopyramide phosphate and other drugs to ischemic areas following coronary occlusion could occur by diffusion from blood bathing the endocardial surface of the left ventricle diffusion from the adjacent normal areas or via collateral blood flow[29, 3] Other factors that probably play a significant role include *local* metabolic enzymatic and morphologic changes[24, 31, 3] in the ischemic zone that would tend to enhance the drug effect Our observation of a slightly greater prolongation of refractory periods in ischemic areas in animals receiving disopyramide phosphate before when compared to those receiving the drug after coronary occlusion (see Table I) could be interpreted to indicate that ischemic areas in the former group had a higher drug concentration The fact that in both protocols changes in refractory periods and conduction times were greater in ischemic areas when compared to nonischemic areas, notwithstanding the probability that drug concentration was lower in the former areas tends to indicate that local changes in the ischemic areas potentiated the drug effect Further clarification

of the aforementioned hypothesis warrants additional studies

Summary

In order to correlate the antiarrhythmic and electrophysiological effects of disopyramide phosphate during acute myocardial ischemia we performed experiments in 17 mongrel dogs. Refractory periods obtained by the extrastimulus method and conduction times recorded from local electrograms were determined in potentially ischemic and nonischemic areas prior to after left anterior descending coronary occlusion and following intravenous administration of disopyramide phosphate 3 mg/Kg. Control refractory periods were similar in both nonischemic and ischemic areas. Following coronary ligation a disparity of refractoriness of 28 msec was induced between these two areas. After disopyramide administration this disparity was reduced from 28 msec to 5 msec ($p < 0.001$) after 5 to 15 minutes and to 15 msec ($p < 0.01$) after 15 to 30 minutes. Coronary ligation prolonged conduction times by 8 msec ($p < 0.005$) in ischemic areas and disopyramide further prolonged conduction in these areas by an additional 9 msec ($p < 0.001$). A minimal and transient prolongation of conduction was present in nonischemic areas. We conclude that the differential effects exerted by disopyramide phosphate in ischemic areas may explain its suppressant action on arrhythmias of ventricular origin.

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Elevation of ventricular defibrillation threshold in dogs by antiarrhythmic drugs

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The minimum electrical dose in terms of either current or energy required to defibrillate the ventricles is defined as the ventricular defibrillation threshold Although there are many reports of the influence of antiarrhythmic drugs on fibrillation threshold there are no quantitative studies which have shown the effect of such drugs on the minimum energy or current required to defibrillate the ventricles This paper describes a new phenomenon the elevation of ventricular defibrillation threshold by three antiarrhythmic drugs

Drug effects upon defibrillation threshold are of potential clinical importance because patients who fibrillate may have been placed on maintenance antiarrhythmic drug therapy or admitted to coronary care units where antiarrhythmic drugs may be given routinely A population of patients especially prone to sudden death may be identified[1] for whom some authors have proposed prophylactic treatment with procainamide or related drugs in selected cases Intravenous lidocaine by bolus injection or continuous infusion is currently recommended for hospitalized patients following acute myocardial infarction in order to prevent ventricular fibrillation[3, 4] Nonetheless the ventricles of patients receiving lidocaine may still fibrillate[7] During cardiopulmonary resuscitation a variety of drugs may be given prior to defibrillation

Since some authors have indicated that present commercial defibrillators which store 400 watt seconds of energy may have marginal or inadequate output for heavyweight patients[8] the question of whether antiarrhythmic drugs alter the electrical dose required for defibrillation becomes especially pertinent Accordingly the present study was conducted to determine if antiarrhythmic drugs alter ventricular defibrillation threshold in a stable animal model

Methods and materials

Twenty five mongrel dogs weighing 6 to 12 kilograms and anesthetized with pentobarbital sodium (30 mg/Kg intravenously) served as subjects This anesthetic was chosen because we have previously shown that it does not alter the defibrillation threshold[1] The details of anesthesia and monitoring have been described previously In brief fibrillation was induced by 60 Hz electrical stimulation of the right ventricle via an intracardiac catheter–electrode Defibrillation threshold was determined by repeated trials of fibrillation and transchest defibrillation with successive damped sinusoidal defibrillator* shocks each of peak current amplitude 10 per cent less than the amplitude of the preceding

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*Capa tance 16 microfarads induct nce 44 millih nrys internal resist nce ohms

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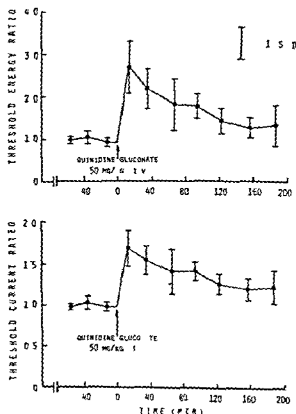


Fig 1 Effect of intravenous quinidine on ventricular defibrillation threshold in five dogs The absolute threshold values corresponding to 1 00 on the vertical axes were 0 94 w s/Kg and 1 21 A /Kg All threshold elevations after quinidine injection are statistically significant (U < 11 p < 0 01) except the final data point at 18^ minutes Becau e of the difference in the standard deviations of pre-drug and post-drug data the Mann Whitney U test of significance was used to compare post-drug values with the aggregate pre-drug control values in this and ubsequent figures

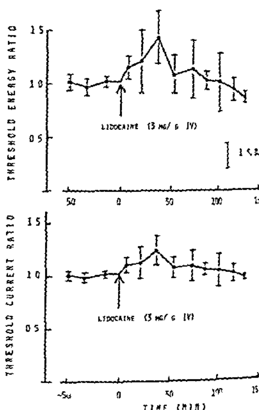


Fig 2 Effect of intravenous lidocaine on ventricular defi[illegible] lation threshold in five dogs The absolute threshold va[illegible] corresponding to 1 00 on the vertical axes were 0 83 w s and 1 16 A /Kg The peak elevation in defibrillation thres[illegible] is statistically significant (U < 11 p < 0 01)

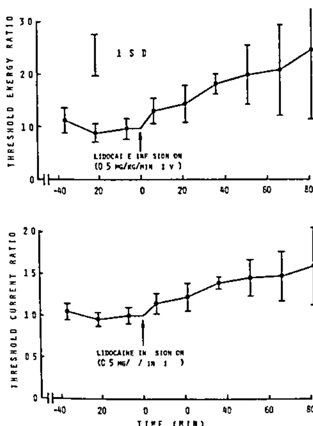
shock The lowest shock intensity able to achieve defibrillation and differing no more than 10 per cent in amplitude from an intensity which did not defibrillate was defined as threshold

The ventricles never were permitted to fibril late more than 30 seconds prior to defibrillation and never were refibrillated until arterial blood pressure had returned to a stable level The peak voltage and peak current for e[illegible]h shock were recorded [illegible]n a storage o[illegible]pe Only data from the first shocks applied after the onset of ventricul[illegible] fibrillation were [illegible] [illegible]he calcula tion of th[illegible] [illegible] Delivere[illegible] [illegible] calcu lated from [illegible]he product of [illegible] [illegible] peak current and [illegible] fibrillation [illegible] previously described

The antiarrh[illegible] [illegible] dru[illegible] [illegible] th[illegible] [illegible]udy were quinidine gl[illegible]conate inje[illegible] [illegible] (Lilly)

80 mg /ml lidocaine hydrochloride inject (Astra) 20 mg /ml pH 6 7 and 5 5 diphenyl dantoin sodium salt (Sigma Chemical Co Louis Mo) A freshly prepared alkaline solut of diphenylhydantoin in water was used beca the usual commercial diluent has been shown alter the threshold for electrical stimulation cardiac tissue [11] Quinidine was given as a sin intravenous bolus (50 mg /Kg) to five dogs Li caine was given as single intravenous bolus mg /Kg) to five dogs and as a constant infus (0 5 mg /Kg /minute) to another five dogs I phenylhydantoin was given as a continuous in sion (1 mg /Kg /minute) to an additional f dogs These antiarrhythmic drug doses are in t range of 0 7 to 7 times the recommended the peutic doses for dogs Five dogs in a conti group received no drug other than pentobarbi to determine the effect of repetitive trials on t defibrillation threshold

In all groups ventricular defibrillation thre old was determined at 15 minute interval befo



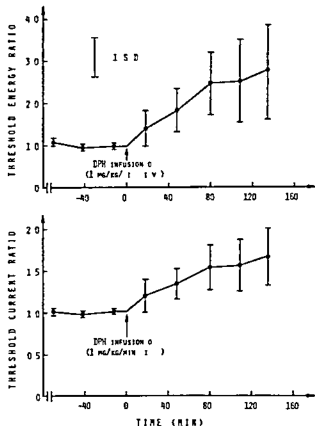


Fig 3 Effect of lidocaine infusion on ventricular defibrillation threshold in five dogs The absolute threshold values corresponding to 1 00 on the vertical axes were 0 67 w s/Kg and 1 00 A /Kg. All threshold elevations after onset of the infusion are statistically significant (U < 14 p < 0 05) After 30 minutes of infusion threshold elevations are highly significant (U < 11 p < 0 01)

Fig 4 Effect of diphenylhydantoin *(DPH)* infusion on ventricular defibrillation threshold in five dogs The absolute threshold values corresponding to 1 00 on the vertical axes were 0 76 w.s/Kg and 1 01 A /Kg All threshold elevations after onset of the infusion are statistically significant (U < 11 p < 0 01)

and after drug treatment The mean of three pre-drug threshold values for each animal was defined as 100 per cent of control and served as the reference for drug effect

Results

Fig 1 shows the dramatic elevation of the threshold current and energy caused by an intravenous bolus of quinidine gluconate (50 mg quinidine base/Kg) in five dogs The data points in Fig 1 represent mean threshold energy and current ratios which were calculated by dividing the individual threshold values by the average reference value for each animal The period of negative time on the abscissa represents this control period Quinidine increased threshold peak current by 70 per cent and threshold delivered energy by 172 per cent The dose of quinidine was sufficient to cause blood pressure to fall initially from average values (systolic/mean/diastolic) of 170/140/128 mm Hg to 95/73/60 mm Hg Thereafter the magnitude of blood pressure depression gradually diminished at approximately the same rate as the magnitude of defibrillation threshold elevation

Fig 2 illustrates a similar elevation of defibrillation threshold by an intravenous bolus of lidocaine (3 mg /Kg) The maximal elevation of threshold current was 26 per cent and the maximal elevation of threshold energy was 48 per cent The peak effect of lidocaine appeared later than the peak effect of quinidine Administration of lidocaine by continuous intravenous infusion (0 5 mg /Kg /minute) also caused threshold to increase steadily in another group of five dogs

These high control blood pressures are characteristic of dogs anesthetized with pentobarbital.

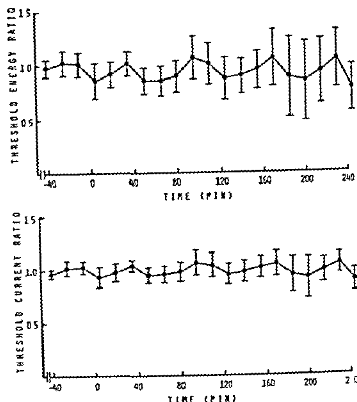


Fig 5 Effect of pentobarbital anesthesia only on ventricular defibrillation threshold in five dogs The absolute threshold values corresponding to 1 00 on the vertical axes were 0 89 w.s/Kg and 1 1? A /Kg These animals served as controls The slight periodic variations in these threshold data were not reproducible in other control series.

(Fig 3) to a maximum of 199 per cent of control energy and 145 per cent of control current after 80 minutes Blood pressure fell from 158/137/117 mm Hg at the beginning to 137/119/103 mm Hg at the end of the lidocaine infusion

The effect of a continuous infusion of diphenyl hydantoin (DPH) (1 0 mg /Kg /minute) is shown in Fig 4 This agent also caused the defibrillation threshold to increase The increase in threshold was accompanied by a decrease in systolic mean and diastolic blood pressure from 185/160/132 mm Hg to 112 87 60 mm Hg during the DPH infusion

Fig 5 illustrates mean threshold energy and current in the control animals which received only pentobarbital These animals were studied for a longer period of time than any drug treatment group to evaluate the stability of the preparation In these animals threshold energy decreased by about 10 per cent during the first hour of testing and thereafter remained stable Threshold current did not change over a period of 280 minutes and blood pressure remained stab[le] indicating little effect of the repeated episodes [of] fibrillation circulatory arrest and defibrillati[on] upon the dependent variables of this study

These high control blood [pressures are typical] of dogs anesthetized with pentobarbital

Discussion

The objective of the present studies was [to] establish the direction of changes in ventricu[lar] defibrillation threshold produced by antiarrhy[th]mic drugs Some individuals might believe a pr[iori] that drugs given clinically to prevent fibrillat[ion] would also make defibrillation of the heart ea[sier] Others might speculate that since most ant[iar]rhythmic drugs reduce the excitability of car[diac] muscle and since defibrillation is caused by de[po]larization of cardiac muscle most antiarrhyth[mic] drugs would elevate the defibrillation thresh[old]

The only previous report of the influence o[f] antiarrhythmic drug upon ventricular defibr[illa]tion is that of Woolfolk and associates[.] [They] found that quinidine (10 to 60 mg /Kg intr[ave]nously) decreased the likelihood of succe[ssful] ventricular defibrillation in dogs given transc[hest] shocks of 30 40 or 50 watt seconds The pre[sent] studies confirm Woolfolk and colleagues con[...]

sion and also demonstrate that failure to defibrillate in the presence of quinidine may be reversed by the use of increased electric shock strength

In the present study relatively large doses of three antiarrhythmic drugs were used to demonstrate the phenomenon that antiarrhythmic drugs may raise the defibrillation threshold The doses employed however did not cause mean blood pressure to fall below 70 mm Hg and in this sense were pharmacologic rather than toxic Plasma levels of quinidine lidocaine and diphenylhydantoin were not obtained in this initial study since the pharmacokinetics of animals subjected to repeated ventricular fibrillation and defibrillation are complex and equilibration of drug between plasma and tissue compartments could not be assumed Under the conditions in which the experiments were performed it is likely that plasma drug levels which might have been obtained would have been falsely high or grossly out of phase with the physiologic response Indeed the peak elevation of defibrillation threshold after an intravenous bolus of lidocaine occurred 40 minutes after injection in intact dogs although peak plasma levels must have been established within seconds Nonetheless the present study points toward the potential practical importance of drug induced elevations in ventricular defibrillation threshold in situations when defibrillator output is marginal

Pantridge and associates Tacker and colleagues and Collins and co workers have reported that in patients weighing over 100 kilograms ventricular fibrillation often is not abolished by maximal (400 stored watt second) shocks from typical clinical defibrillators In comparably heavyweight animals shocks in excess of 400 watt seconds increased the per cent success in defibrillation Presumably the defibrillation thresholds of heavyweight patients are already close to the shock strength provided by 400 stored watt seconds In such individuals drug induced elevations of defibrillation threshold could be lethal

There is at present controversy about the appropriate shock strength for human ventricular defibrillation The shock strength required for a given per cent success reported by Adgey and colleagues and by Crampton and co workers for out of hospital ventricular defibrillation is considerably less than the shock strengths reported by Tacker and associates for a population of hospitalized patients One possible explanation for the discrepancy between these studies may be more intensive antiarrhythmic drug therapy in the hospitalized patient group Accordingly closer attention to drug treatment is warranted in future studies of human ventricular defibrillation

Summary

Effects of antiarrhythmic drugs upon the threshold delivered energy (TDE) and threshold peak current (TPC) for electrical ventricular defibrillation by damped sinusoidal shocks were investigated in 25 pentobarbital anesthetized dogs TDE and TPC were increased by the three antiarrhythmic drugs tested Bolus injections produced a transient rise and continuous infusions produced a steady rise in defibrillation threshold The maximal percent elevations in mean defibrillation threshold during the 60 minutes after intravenous drug treatment in groups of n = 5 dogs were

Table I

Treatment	*% ↑ in TDE*	*% ↑ in TPC*
Lidocaine bolus (3 mg /Kg)	48	26
Lidocaine (0 5 mg./Kg /min.)	99	45
Quinidine bolus (50 mg /Kg)	172	70
Diphenylhydantoin (1 mg / Kg /min)	83	35
Controls	1	4

Accordingly individuals receiving antiarrhythmic drugs who nonetheless fibrillate may require greater electric shock strength for defibrillation

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Effect of glucose–insulin–potassium solution on the exercise performance of patients with coronary artery disease*

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Solutions containing glucose insulin and potassium (GIK) are considered beneficial in myocardial ischemia Proposed mechanisms of action include restoration of the intracellular concentration of potassium change of the membrane potential to more normal levels decrease in arrhythmias acceleration of wound healing and decreased lysosomal activity Increased availability of glucose is thought to be beneficial to the ischemic cell by providing energy through anaerobic glycolysis[6] In addition glucose-insulin-potassium solutions suppress the levels of circulating free fatty acids (FFA) which have been linked to increased incidence of ventricular arrhythmias increased myocardial oxygen consumption and decreased contractility It is assumed that GIK may exert a beneficial effect by substituting glucose for FFA as substrate Others have suggested that GIK may be beneficial through an osmotic effect to decrease edema improve compliance and increase contractility However in spite of these considerations diversity of opinion exists on the effectiveness of GIK solutions in decreasing the complications and mortality of acute myocardial infarction [3 9] Similarly conflicting reports have appeared on the effect of GIK and FFA in patients with coronary artery disease at rest and during stress induced by atrial pacing [3] We studied the effect of GIK during exercise in patients with angiographically documented coronary artery disease The results suggest a deleterious rather than a beneficial influence of GIK in this setting

Material and methods

Nine patients (seven men and two women) aged 50 to 69 years (mean 54 years) with coronary artery disease documented by coronary arteriography were enrolled in the study The minimum criterion for inclusion in the study was stenosis of at least one major coronary artery compromising the lumen by more than 70 per cent Seven patients had a history of acute myocardial infarction seven had angina and five had both angina and a history of myocardial infarction Three patients had coronary artery disease limited to one vessel two patients had disease in two vessels and four patients had three vessel disease One patient had severe left ventricular impairment (ejection fraction 0.26 marked hypokinesis of the anterior apical and inferior aspects of the ventricle as visualized in the right anterior oblique projection) two patients had hypokinesis of two segments four patients had hypokinesis of one segment and two

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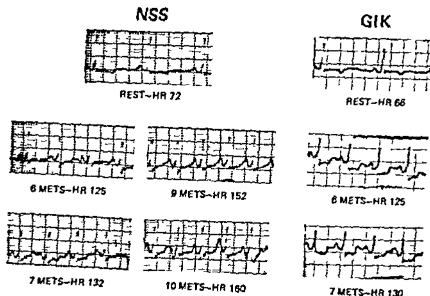


Fig 1 Effect of GIK on the electrocardiogram (Lead MCL) during exercise stress in a patient with coronary artery disease NSS = saline control Note the occurrence of ST depression of the ischemic type in GIK at 6 and METS while this did *not occur at similar* or higher rates and exercise levels (6 7 9 and 10 METS) in control ST segment at rest is similar in GIK and NSS

patients had normal ventriculograms The patients were not on nitrates propranolol diuretic or antiarrhythmic agents during the period of the study and did not have diseases other than coronary artery disease No one had significant hypokalemia (mean serum potassium 4 4 mEq / L range 3 5 to 4 8 mEq /L) A complete history, physical examination chest x ray urinalysis complete blood count biochemical screen and coronary arteriography were performed and an informed consent was obtained A continuous multi stage exercise stress test was performed twice in the postabsorptive state in order to familiarize the patients with the procedure One week later the patients were exercised on a motor driven treadmill at a speed of 3 miles per hour and a grade that was increased by 2.5 per cent every three minutes until severe angina or marked (0.3 mV more than any ST depression noted at rest) ST depression was noted or until they were unable to continue due to excessive fatigue Modified Lead V (CM 5) was monitored The blood pressure was measured at the end of each phase of exercise A 12 lead electrocardiogram was obtained prior to and immediately after the end of exercise and every two minutes thereafter for ten minutes Since GIK may affect the repolarization phase of the electrocardiogram the ST segment of the tracings obtained during and after exercise was compared to the ST segment at rest The exercise test was considered positive if additional horizontal or downsloping ST depression exceeding 0 1 mV was caused by exercise.

The patients were exercised on consecutive days during infusion of a solution according to the following three protocols in randomized sequence

1 Intravenous injection of a 50 ml bolus followed by infusion at a rate of 1 ml/Kg /hr of 30 per cent glucose in water with 80 mM /L of KCl and 50 units of regular insulin

2 Injection of a 50 ml bolus of normal saline followed by infusion of normal saline at a rate of 1 ml /Kg /hr

3 No infusion (control) The solutions were administered through an indwelling catheter inserted in the antecubital vein Blood samples were obtained prior to the onset of infusion during exercise at 5 METS and at the end of exercise through another catheter inserted in the other antecubital vein METS metabolic equivalents corresponding to multiples of the consumption at rest (3 5 ml O /Kg /minute) were estimated from the speed and grade of the treadmill.[15] Serum potassium was determined by flame photometry standardized with lithium (according to the method of Beckman) Serum FFA were determined by allowing the copper salt of FFA to react with 2 2 thiazolylaso para cresole (following the method of Noma and colleagues) Serum glucose was determined by a procedure utilizing the potassium ferricyanide potassium ferrocyanide

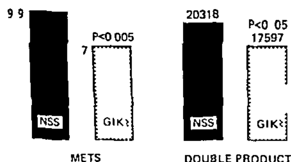


Fig 2 Effect of GIK on exercise tolerance of nine patients with coronary artery disease Note that the exercise tolerance diminished as evidenced by lower work and lower double product (Heart Rate × Blood Pressure) at the end of exercise

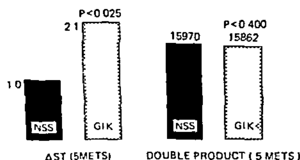


Fig 3 Effect of GIK on exercise induced ST depression in nine patients with coronary artery disease Note that at the same exercise level and similar double product the ST depression was more pronounced after GIK infusion than after NSS

nide oxidation reduction reaction (Technicon Autoanalyzer Methodology) Serum lactate was determined utilizing lactate dehydrogenase following the formation of NADH The physician performing the stress test was unaware of the type of the infusate The data were analyzed in a blind fashion by two cardiologists not participating in the exercise testing The magnitude of ST depression heart rate × blood pressure product arrhythmia and the above biochemical parameters at 5 METS and at the end point were compared for the three groups of experiments using Student s test for paired comparison

Table I Effect of GIK saline and control on exercise test in nine patients with coronary artery disease

	C	NSS	GIK
Angina	7	7	8
Positive test	6	6	8
Marked ST depression	2	2	3
Severe angina	3	3	4
Excessive fatigue	4	4	3

Hori ntal o down loping ST d pression exceeding any ST d pression present at rest by more than 0 1 mV
Horizontal or downsloping ST depression e ceeding any ST d pression present at rest by more than 0 3 mV
Necessitating interruption of the ex rcise

Results

The results are summarized in Tables I and II and in Figs 1 to 6 There were no significant differences in end points exercise tolerance heart rate blood pressure or the electrocardiogram between control and saline experiments

1 Angina The end points that prompted the cessation of exercise were similar in control saline and GIK experiments In control and saline experiments the exercise test was stopped because of severe angina in three patients excessive fatigue in four patients and ST depression exceeding any ST depression present at rest by at least 0 3 mV in two patients These two patients also developed angina during the exercise test The test was interrupted before the occurrence of severe angina because of the associated electrocardiographic changes In two other patients angina occurred during the exercise test which was interrupted because of excessive fatigue Angina occurred in seven patients during the control and saline experiments and in eight patients during infusion of GIK In the seven patients who had angina in saline experiments this symptom appeared earlier when the patients were exercising during GIK infusion (6 4 ± 1 4 METS compared to 9 9 ± 3 4 METS in saline experiments $p < 0\,01$) In one additional patient the exercise was interrupted because of angina associated with 0 3 mV ST depression during infusion of glucose–insulin–potassium solution while angina was not observed and the exercise was terminated at a higher level because of fatigue in control and saline experiments The

Table II Effect of GIK on exercise performance of nine patients with coronary artery disease

Pt no	I	Exer level (METS) End point	Exer level (METS) Angina onset	BP × HR (mm Hg min) 5 METS	BP × HR (mm Hg min) End point	Δ ST (5 METS 0 1 mV)	Glucose mg /100 ml Pre exer	Glucose mg /100 ml 5 METS	Glucose mg /100 ml End point	Free fatty ac μEq/L. Pre exer	Free fatty ac μEq/L. 5 METS
1	NSS	12	12	17850	29640	1	120	122	118	330	2 0
	GIK	5	5	19200	19200	4	125	186	186	660	450
2	NSS	9	8	14300	21450	1	111	112	100	5?0	960
	GIK	9	7	13440	20160	1	97	368	300	8,0	300
3	NSS	16	15	15250	18900	0	134	103	116	2?0	1,30
	GIK	10	8	18200	18000	0	111	276	145	4 0	710
4	NSS	6	6	14040	15930	3 5	154	152	174	309	407
	GIK	5	5	15600	15600	6	149	209	180	23?	111
5	NSS	14	13	27000	29450	1	117	122	123	510	2900
	GIK	9	8	26225	2922?	1	119	195	120	2040	12 0
6	NSS	9	8	12960	14000	1.5	118	116	115	3,0	940
	GIK	8	7	12375	13375	2	106	133	79	,?0	?10
7	NSS	7	7	9375	16000	0	113	109	133	280	600
	GIK	5	5	10320	10320	1	135	2?6	243	?40	8?0
8	NSS	9	—	19840	23120	0	96	9?	96	380	111
	GIK	7	7	19900	21000	1.5	68	249	247	554	145
9	NSS	7	—	13120	14375	1.5	88	88	92	208	303
	GIK	5	—	11500	11500	2.5	78	16?	167	225	49

Intervention.
Marked ST depression (more than .3 mV)
Ang = angina Fatg = fatigue

remaining eight patients had the same end point in all three types of experiments

Six patients had positive stress test (horizontal or downsloping ST depression exceeding any ST depression present at rest by at least 0 1 mV) in saline and control experiments and three had a negative test In two of the latter the test became positive during infusion of GIK (Table I Fig 1)

2 Physiological variables After infusion of GIK the exercise tolerance decreased in eight patients and remained unchanged in one For similar end points as described above the average exercise level at the end of exercise was 9 9 ± 3 4 METS in saline experiments and 7 ± 2 1 METS in GIK experiments ($p < 0\ 005$) In addition the product of heart rate and systolic blood pressure at the end of exercise was significantly lower in GIK (17597 ± 5788 mm Hg min) than in saline experiments (20318 ± 6068 mm Hg min $p < 0\ 05$) (Fig 2) When the patients were compared at the same level (5 METS) a more pronounced ST depression was noted in GIK (0.21 ± 0 11 mV) than in saline experiments (0 mV ± 0 18 $p < 0\ 025$) in spite of similar double products (Figs 3 to 5)

3 Biochemical measurements In saline experiments an increase in serum FFA (by 566 ± 8 μEq/L at 5 METS and 650 ± 996 μEq/L at end point) lactate (by 5 1 ± 6 8 mg per cent at 5 METS and 12 1 ± 7 8 mg per cent at end point) and potassium (by 0 21 ± 0 39 mEq /L at 5 METS and 0 43 ± 0 38 mEq /L at end point) occurred with exercise while no significant change in serum glucose was observed On the other hand the response of these variables to exercise during GIK infusion was different Compared to saline experiments a significant decrease rather than an increase in FFA (by 272 ± 400 μEq/L, $p < 0\ 025$ at 5 METS and by 197 ± 246 μEq/L, $p < 0\ 05$ at end point) was observed Similarly a decrease rather than an increase in serum potassium concentration (by 0 11 ± 0.23 mEq /L, $p < 0\ 05$ at 5 METS and by 0 15 ± 0.24 mEq/L, $p < 0\ 001$ at end point) was seen A significant increase in blood sugar (by 116 ± 75 mg /100 ml.

Potassium mEq /L			*Lactate mg /100 mL*			
Pre exer	*5 METS*	*End point*	*Pre exer*	*5 METS*	*End point*	*Obser*
4.3	4.2	5	16 5	10 5	18 6	Ang MST[a]
4.5	4.3	4.3	10 7	13.2	20 6	Ang MST[a]
4.2	4 0	4.9	9 4	17.3	23.2	Ang
4 0	4 1	4.3	15 7	19 7	19 7	Ang
4 1	4.5	5 0	23.3	31.5	41 4	Ang
4 3	4 1	4.3	13 7	21 1	47 1	Ang
4.3	4.5	4.5	10 1	23 6	23 6	Ang Fatg
4 1	4.3	3.9	11 4	22 1	22 1	Ang Fatg
4.9	5.2	5 7				Ang
4 7	4.2	4.2				Ang
4 8	4 7	4.8				Ang MST
4 6	4 6	4.5				Ang MST
5 0	6 1	4.8				Ang Fatg
4 4	4.2	4 0				Ang Fatg
3.5	3.5	3 9	9 1	13 9	30.9	Fatg
3.5	3 6	3 6	11.2	22.8	33.3	Ang MST[a]
4 6	4.9	5 0	13 1	15 1	16.5	Fatg
4.5	4.2	4 1	12 4	16 6	16 6	Fatg

$p < 0\ 005$ at 5 METS and by 73 ± 74 per 100 ml $p < 0\ 01$ at end point) was seen in GIK but not in control experiments Although a more pronounced change in lactate concentration was seen on GIK experiments than in saline this was not statistically significant (Fig 6) These differences between saline and GIK were observed both while patients were exercising at the same exercise level (5 METS) and at the end of exercise when on the average they were exercising at a lower level during GIK experiments

4 **Arrhythmias** The incidence of arrhythmias observed in this study was not high enough to allow us to reach firm conclusions One patient developed premature atrial contractions during NSS and one developed them during GIK experiments One patient developed premature ventricular contractions in saline experiments and three patients (i e two additional patients) developed premature ventricular contractions during GIK infusion This tendency of GIK to induce more arrhythmias would appear to be more pronounced if the shorter sampling period due to the shorter duration of exercise in the GIK group is taken into consideration However the total number of premature beats recorded was too small to allow reliable statistical analysis

Discussion

We were unable to demonstrate a beneficial effect of GIK on the exercise performance of patients with coronary artery disease Infusion of GIK actually resulted in a decrease of both the total time of exercise and the maximum workload in eight out of nine patients It is unlikely that this decrease in exercise tolerance after GIK was due to subjective factors since the patients had been familiarized with the procedure prior to the study the endpoints were similar the sequence of the studies was randomized and neither the physician performing the study nor the patients knew the content of the infusate Moreover at the end of exercise the product of systolic blood pressure and heart rate an accepted index of myocardial oxygen consumption was lower in GIK experiments than in saline controls[36,37] In addition angina occurred earlier (at a lower exercise level) after infusion of GIK than in control These considerations suggest that GIK modified the exercise performance by an effect on the heart rather than on the musculoskeletal system This opinion is further supported by the fact that in two patients the stress test became positive (exercise induced horizontal or down sloping ST depression exceeding any ST depression noted at rest by more than 0 1 mV) after GIK infusion while it was negative in control and by the more pronounced ST depression induced by GIK (compared to saline) that was observed when all patients were exercising at the same level (5 METS) and were having similar double products

The exact mechanism responsible for the apparently impaired cardiac performance during exercise after GIK infusion is not known A possible explanation may be found in the changes observed in biochemical parameters In control experiments an increase in serum FFA lactate and potassium was induced by exercise No change in blood sugar occurred in this group These changes are similar to those previously reported and are probably due to catecholamine induced lipolysis and to release of lactate and potassium from skeletal muscle[3-40] On the other hand in the GIK group an increase in blood sugar (averaging 116 ± 75 mg per 100 ml $p < 0\ 005$ at

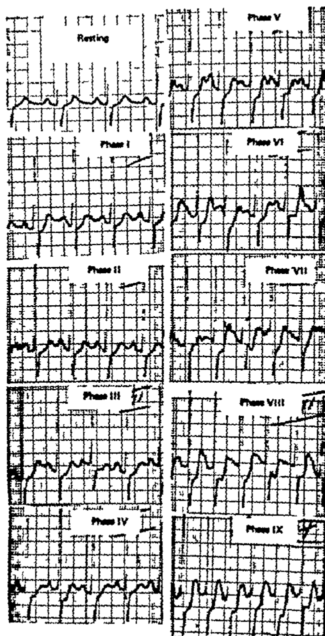


Fig 4 Effect of GIK on the exercise tolerance and electrocardiogram f a patient with coronary artery disease NSS study Note that patient was able to exercise for nine phases (12 METS) corresponding to 27 minutes The exercise was discontinued because of angina and marked ST depression

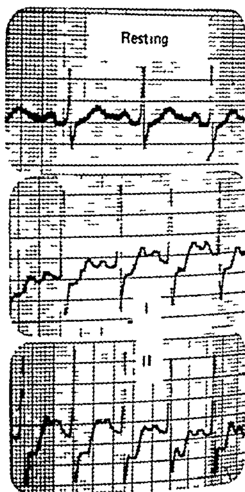


Fig 5 Same patient as *Fig 4* GIK study Note the marked decrease in exercise tolerance The exercise was discontinued after 6 minutes or two phases (5 METS) because of angina accompanied by marked ST depression

5 METS and 73 ± 74 mg per 100 ml $p < 0.01$ at end point) was observed In addition a decrease in serum FFA probably resulting from inhibition of release and increased esterification in adipose tissue and a decrease in serum potassium were noted [1] It has been suggested that in the presence of myocardial infarction infusion of GIK results in marked decrease in utilization of FFA while the required energy is derived from increased uptake of glucose Other studies have shown that FFA represent a major substrate for oxidation by the myocardium during exercise [7] Data obtained in this investigation may be interpreted as indicating that in spite of increased glucose availability with GIK infusion the heart cannot perform at the high work loads imposed by exercise without optimal metabolic support from FFA [43] [8] Although the increase in serum lactate associated with exercise was more pronounced in the GIK than in saline experiments this difference was not statistically significant

Metabolism of FFA by ischemic myocardium is considered undesirable since it may be associated with increased myocardial oxygen consumption and depressed myocardial mechanical performance while increased glucose availability is considered beneficial since it may increase energy

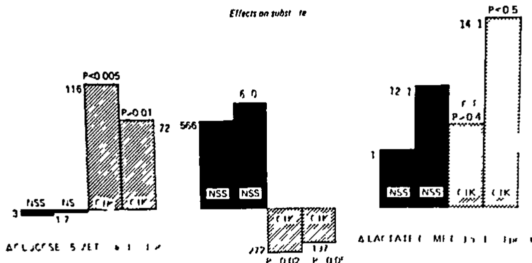


Fig 6 Effect of GIK on serum glucose (mg /100 ml) FFA(μEq/L.) and lactate (mg /100 mL) during exercise in patients with coronary artery disease Mean difference of values at 5 METS (*left columns*) and at the end of exercise (*right columns*) from pre-exercise values

production by anaerobic glycolysis and polarize the membrane by increasing intracellular potassium concentration However there is reason to believe that anaerobic glycolysis in poorly perfused parts of the heart would result in lactate and H+ accumulation which would limit the glycolytic flux and could be harmful per se In addition FFA do not cause an increase of myocardial oxygen consumption in patients with coronary artery disease at rest or during atrial pacing [33,34] and convincing evidence that GIK drives potassium into the ischemic myocyte is lacking [49,50] These considerations would generate doubt as to whether GIK could significantly improve the function of the ischemic myocardium

It is possible that the decrease in exercise performance after GIK reported here is due to decreased availability of FFA to the perfused (normal) parts of the heart in turn resulting in energy production inadequate for the increased needs imposed by exercise It is also possible that the GIK might have worsened the exercise tolerance of our patients by an osmotic effect resulting in an elevated left ventricular end diastolic pressure GIK containing 30 per cent glucose is expected to create more pronounced osmotic effects than the equal volume of NSS that was used as control Serum and intracellular potassium concentrations are intimately involved in genesis of the electrocardiogram and a decrease or increase of serum potassium concentration may be produced by infusion of GIK In our study a small but consistent decrease in serum potassium was noted This modest change might have contributed to the more pronounced ST T changes seen during GIK infusion but it is unlikely that it is the cause of the decreased exercise tolerance and earlier occurrence of angina

Ineffectiveness of GIK in improving cardiac function during stress has been also reported by Lesch and associates [3] who found diminished tolerance to pacing induced angina in spite of augmented myocardial glucose uptake after infusion of GIK On the other hand Chiong and associates[3] reported a protective effect of GIK on the response to atrial pacing We are not aware of other studies on the effect of GIK on exercise stress in patients with coronary artery disease Oliver and colleagues have reported that the ST depression induced by exercise in patients with angina was less when a nicotinic acid analog which acts to suppress FFA was given There was however no difference of the length of time the patients could exercise before the onset of angina [5] This study cannot be easily compared to that of ours since insulin glucose and potassium were not administered and an osmotic or metabolic effect of these substances may be important In the present study no significant effect of GIK on the incidence of arrhythmias was observed This would speak against a direct arrhythmogenic effect of free fatty acids in patients with chronic

coronary artery disease Although FFA are considered arrhythmogenic[14,15] Opie and associates[5] reported a failure of high concentrations of FFA to provoke arrhythmias in experimental myocardial infarction and we found that marked elevation of FFA induced by infusion of fat and heparin did not affect the ventricular fibrillation threshold in dogs with acute myocardial infarction[33]

In summary we were unable to demonstrate a beneficial effect of GIK infusion during exercise stress in patients with coronary artery disease On the contrary, a decrease in exercise tolerance and earlier occurrence of angina were noted Further definition of the operative mechanisms requires measurements of coronary blood flow, A V differences of substrates oxygen, and potassium more detailed hemodynamic studies, and larger numbers of patients However, our data raise the speculation that GIK may have undesirable effects in patients with myocardial infarction and aortic stenosis hypertension congestive heart failure or arrhythmias conditions that may increase myocardial energy requirements Based on the data presently available we believe that it is inappropriate to accept GIK as a routine therapeutic modality in coronary artery disease

Summary

Treadmill exercise testing was performed in double blind fashion on nine untrained non diabetic subjects with angiographically proven coronary artery disease and stable exercise tolerance They were exercised on three different days in randomized sequence as follows With infusion of 30 per cent solution of glucose in water containing 50 units of regular insulin and 80 mM of KCl per liter 50 ml bolus followed by 1 ml /Kg /hr (GIK) with infusion of normal saline, (NSS) 50 ml bolus followed by 1 ml / Kg /hr and without infusion (control) There were no significant differences between control and saline experiments

A decrease in work capacity (9 9 ± 3 4 to 7 0 ± 2 1 METS p < 0 005) and the product of the heart rate and systolic blood pressure (20318 ± 6068 to 17597 ± 5788 mm Hg min ' p < 0 05) at the end of exercise was observed in *GIK experiments Angina occurred at lower exercise levels* in GIK studies (6 4 ± 1 4 METS) than in NSS studies (9 9 ± 3 4 METS p < 0 01) When compared at the same exercise level (5 METS) more pronounced ST depression (0.21 ± 01 mV) was seen in GIK than in NSS stud (0 1 ± 0 18 mV p < 025) *In two patients th exercise test was negative in NSS and becam positive in GIK*

In GIK, a decrease in serum FFA compared t resting level was noted at the end of exercis (197 ± 246 μEq/L) and during exercise at METS (272 ± 400 μEq/L) as opposed to a increase (566 ± 853 μEq/L, p < 0 025 at 5 MET and 650 ± 996 μEq/L p < 0 05 at the end o exercise) in NSS An increase in blood glucos (73 ± 74 mg /100 ml, p < 0 01) at the end o exercise and (116 ± 75 mg /100 ml p < 0 005) a 5 METS was noted in GIK but not in NS studies A small decrease in serum potassium (b 0 11 ± 0 23 mEq /L at 5 METS and b 0 15 ± 0 24 mEq /L at the end of exercise) wa seen in GIK but an increase in the saline grou (by 0 21 ± 0.39 mEq /L p < 0 05 at 5 MET and by 0 43 ± 0 38 mEq /L p < 0 001 at the en of exercise) No significant differences in serum lactate were noted

The data indicate that GIK diminishes th exercise performance and hastens the onset o angina in patients with coronary artery disease I appears that increased availability of glucose an potassium does not have a beneficial effect in th presence of depressed FFA levels during exer cise

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Case reports

Spontaneous resumption of sinus rhythm in an elderly patient after 13 years of permanent atrial fibrillation

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Almost every heart disease, either structural or secondary to extraneous factors—e.g., hyperthyroidism—can eventually lead to auricular fibrillation, initially paroxysmal then permanent. Notoriously, mitral valve disease has a major propensity for that complication, often at an early stage of its natural history. When established for months or worse, when it has been in evidence for years, atrial fibrillation is held to be definitive. However, from time to time the medical literature reports on spontaneous reversion to sinus rhythm of long standing atrial fibrillation, mostly but not exclusively in mitral patients. Those observations are recognized as very rare, highly intriguing, and hitherto unexplained.[1-4]

I had the opportunity during 24 years of following up a female patient (with moderate pure mitral stenosis, mild hypertensive and ischemic heart disease, and severe pulmonary emphysema) who, after sustaining despite an unnecessary mitral commissurotomy a 13 years long atrial fibrillation, spontaneously resumed normal sinus rythm at age 66 and is maintaining it nine months later.

I felt it worthwhile to report on that case which constitutes one of the unique records on the subject in the world literature.

Case report

G. P., a 44 year old female patient, consulted me for the first time on April 26, 1954, complaining of palpitations with dyspnea and sporadic sternal pain and dry cough on exertion. She had no antecedent of rheumatic fever but was told at eleven years of age that she had mitral valve disease. At age 26 she delivered a girl without special difficulties. She had suffered numerous bouts of acute bronchitis during her childhood and young adulthood and still was a moderate cigarette smoker. Clinical examination disclosed signs of pure mitral stenosis without associated aortic valve disease. Blood pressure was 140/85. The E.C.G. demonstrated sinus rhythm at 72, P wave abnormalities affecting the terminal force—so called "P mitrale"—and normal ventricular electrogenesis. The fluoroscopic cardiac pattern was characteristic of mitral stenosis: slight enlargement of the left atrium, left auricle, and pulmonary conus. In addition, there was evidence of marked pulmonary emphysema on clinical as well as fluoroscopic grounds.

Considering that the mild symptoms on exertion were basically related to the prominent respiratory insufficiency much more than to the slight mitral block, I decided there was no valid indication for mitral commissurotomy.

Five years later on April 6, 1959, the cardiac and pulmonary status was little changed; the symptoms had not definitely worsened although there was a more conspicuous enlargement of the left atrium and pulmonary artery system; the sinus node command still was present at 85, P waves were identical, and ventricular activity was unremarkable on the E.C.G. However, a mild essential arterial hypertension (160 to 180/100 mm. Hg) had developed.

Five years later, on May 2, 1964, the patient was seen in a worsened condition: atrial fibrillation had taken place a month earlier during the course of severe biliary colics complicated by icterus and infection, with a fast ventricular response (130 to 140 beats per minute). X-ray disclosed a frank cardiomegaly at the expense of the left auricle, left atrium, and right chambers with dilatation of hyperactive pulmonary vessels.

Considering the age (54 years) of that mitral patient and according to my constant and heretofore successful habit, I decided not to attempt a futile cardioversion and instead prescribed appropriate digitalization with digitoxin. Six weeks later improvement was so dramatic—ventricular response at 90, striking reduction of cardiac size and pulmonary vessel dimensions and kinetics at fluorescopy—that I permitted a cholecystectomy to be performed, which was held to be mandatory by the liver specialist.

On July 1, 1964, the patient was operated on. Because of respiratory difficulties that arose from the very beginning of the anesthesia, the surgeon—who unfortunately happened to

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be a heart surgeon—decided to stop the abdominal procedure and instead to carry out an emergency mitral commissurotomy although the respiratory problems were certainly resulting much more from the severe pulmonary emphysema than from the modest mitral block (Valves were found supple and the mitral orifice admitted a finger)

Incidentally the necessary gallbladder removal was performed 5 years later without major incidents In passing it is noteworthy to stress that return of sinus rhythm did not reward the superfluous commissurotomy atrial fibrillation persisted on all tracings until 1977

In the meantime a complete and chronic right bundle branch block commenced by March 1970 the mild systemic hypertension did not subside and modest coronary disease appeared without E C G evidence of ischemic myocardial damage but with a new symptom—blockpnea on exertion a painless variant of angina pectoris (Nonetheless that symptom admittedly remained of equivocal significance in this particular patient because she was also afflicted with severe obstructive pulmonary disease secondarily complicated by bouts of bronchospasm)

During the ten years evolution the whole heart had enlarged but there never was evidence of overt decompensation thanks to a continuous although discreet digitalization (0 1 mg digitoxin per day) associated with intermittent diuretic therapy Ventricular response stood around 80 to 90 beats per minute Unfortunately the pulmonary disease precluded use of small amounts of some beta blocking agent which in conjunction with digitalis and diuretics provides such gratifying benefits in those individuals who are meant to live in permanent auricular fibrillation

This was the medical status of my patient—much more disabled by her pulmonary emphysema than by her still compensated complex heart ailments—when in July 1977 at age 67 years without any therapeutic alteration she was found to be in regular sinus rhythm of 90 beats per minute Nine months later on April 14 1978 the heart remained under sinus node command at a rate of 85 to 90 beats per minute (Fig 1) Clinical E C G and x ray features are identical under the same regimen of digitoxin and diuretics Blood pressure is 170/100 Resumption of sinus rhythm has not resulted in clear improvement of her circulatory status although she now feels a little less crippled by dyspnea probably because a new and astute lung specialist is providing better management for her broncho-pulmonary infirmity—and not as a consequence of really improved cardiac performance ascribable to the return of atrial systole

Discussion

So here we have the quite unusual story of a female patient afflicted with a complex heart disease—init all [illegible] and basically pure mild mitral stenosis com[illegible] [illegible]mized by accident—who thereafter became h[illegible]pertensive with coronary artery disease a[illegible]ted with incapacitating *obstructive pu[illegible] [illegible]ease and who at age 54* had developed [illegible] [illegible]trial fibrillation and 13 years later at ag[illegible] [illegible]tiously resumed sinus rhythm without [illegible] [illegible]nible cause and was still sustaining normal rhythm at her last follow up nine months later

Return of sinus rhythm after years of established auricular fibrillation is a very exceptional event especially when the underlying lesion is mitral valve disease [1,4] Resumption of sinus node command has been occasionally observed either spontaneously or through chemical or electrical cardioversion after mitral commissurotomy As a rule however recurrences of atrial fibrillation occur shortly or after several months, and attempts at maintaining normal rhythm look like aimless endeavors so that a wiser medical attitude surely is to let those patients live with definitive atrial fibrillation while slowing down the ventricular response through adequate digitalization associated or not associated with small doses of a beta blocking drug to the end of obtaining a convenient cardiac output in spite of the loss of atrial contribution to the ventricular systole In so doing a vast majority of those patients can enjoy a quite acceptable circulatory equilibrium while being spared the inconveniences and hazards of repeat electric cardioversions and daily prophylactic antiarrhytmic chemical treatment [5] Conversely it happens that the atria start fibrillating in the wake of an otherwise successful mitral commissurotomy The foregoing remarks apply equally to that category of patients

Independently of surgery, the natural fate of mitral patients is to develop atrial fibrillation sooner or later depending on several factors among which severity and duration of mitral disease stand first As a rule very few mitral patients maintain sinus rhythm after the fifth decade be they operated on or not

Generally speaking established fibrillation advances to a more or less prolonged stage—months or years—of transient paroxysmal episodes of fibrillation flutter or so called fibrillo flutter whose termination is either spontaneous or consecutive to cardioversion

Of course mitral valve disease is only the most prominent cause of those major atrial arrhythmias the one that evokes them at a relatively young age However most heart diseases eventually give birth to atrial flutter and/or fibrillation but at a later stage in their natural history—i.e in elderly patients

Admittedly there are distinct features amo

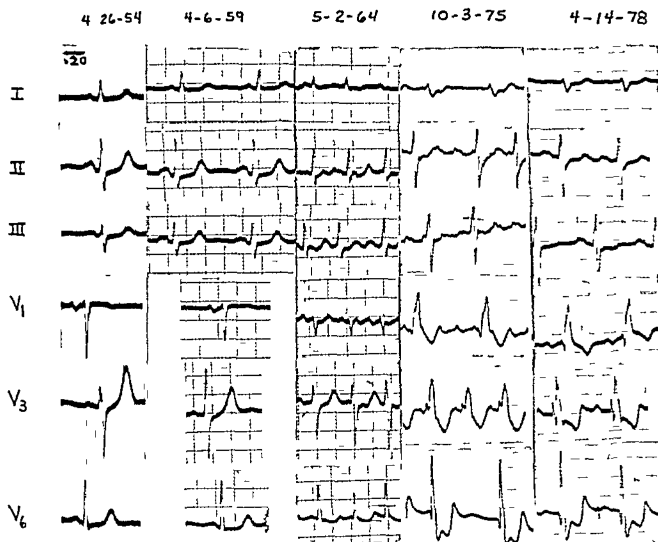


Fig 1 Serial electrocardiogram of patient G P presenting tracings made at intervals over a 24 year period.

these situations Nevertheless the foregoing considerations regarding the course and proper therapeutic attitude in the face of established atrial fibrillation apply as well to these manifestations as they do in mitral patients

Several peculiarities of the present observation deserve emphasis My patient was afflicted not only with pure non tight mitral stenosis but also with mild systemic hypertension of long duration and with coronary artery disease Furthermore she had severe emphysema due to repeat episodes of bronchitis in the remote past aggravated by smoking complicated by asthma and primarily responsible for the dyspnea on effort which increased to an incapacitating point

A mitral commissurotomy performed gratuitously with no necessity did not restore sinus rhythm after hardly 4 months of fibrillation neither did that operation relieve dyspnea on exertion

At age 60 years a complete permanent right bundle branch block appeared attesting to involvement by a probable fibrotic process of part of the ventricular conduction system while atrioventricular connections were spared since the ventricular rate did not slow down

During the last 10 years the four chambers of the heart did enlarge conspicuously showing in particular a large left atrium and a frank augmentation of the left ventricle ascribable to hypertensive and ischemic heart disease in the absence of mitral regurgitation and/or aortic valve involvement

Despite the obvious progressive anatomic dete

rioration and persistence of atrial fibrillation the patient was free of overt decompensation under a constant regimen of moderate digitoxin and diuretics doses (The respiratory distress was clearly linked to increasing pulmonary emphyse ma) The patient developed definitive atrial fibril lation at age 54—which is usual in moderate mitral stenosis—under the direct influence of a severe attack of biliary colic complicated by jaundice and infection while she had never exper ienced prior episodes of transient fibrilla tion—which is unusual During a 13 year follow up serial E C Gs showed various types of abnor mal atrial activity fibrillation (with coarse f waves initially then fine waves in the last years a common finding), flutter fibrillo-flutter, with no noticeable impact on the ventricular rate response

The patient had so well adapted to her irregu lar cardiac action that she had not realized her heart had resumed a regular rate when in July 1977 a routine E C G disclosed the quite unex pected return of sinus rhythm

P waves now are similar in shape and axis to those that were recorded in 1959 and 1964, 18 and 13 years ago It seems worthwhile to stress that the terminal force of P looks identical Moreover there is no impairment in A V conduction The PR interval is consistently unchanged (18 in 1978 16 in 1959) The return of sinus node command took place under the same treatment which had been set up for years namely 10 mg of digitoxin daily and one tablet of a diuretic (Moduretic Merck) 3 days a week

Restoration of sinus rhythm elicited neither a slowing of the heart rate nor overt clinical improvement Circulatory symptoms and signs were unmodified and remain so nine months later with the same doses of digitoxin and diuretics—an additional demonstration in my view of the uselessness of desperately striving to restore and maintain sinus rhythm when a fair and lasting equilibrium can be established thanks to an ele gant digitalization tailored to the precise needs of the individual patient meant for living in chronic auricular fibrillation or flutter whatever the underlying cardiac disease is

In conclusion this report presents one more rare case of spontaneous resumption of sinus node command after more than 13 years of atrial fibrillation in a 67 year old female afflicted with mild mitral stenosis who gratuitously underwent commissurotomy at age 54 The fibrillation [illegible] associated with mild hypertensive and ischem[illegible] cardiomyopathy and with disabling pulmona[illegible] emphysema Nine months later sinus rhyth[illegible] persisted and the circulatory status was stab[illegible] neither worse nor better than before the return [illegible] normal rhythm One challenging question [illegible] mains unanswered how can long standing atr[illegible] fibrillation spontaneously give way to sin[illegible] rhythm when no extraneous factor appe[illegible] responsible for such a basic electrophysiolo[illegible] change?

So far no satisfactory explanation has e[illegible] been exposed Holzmann s theory[8] might be t[illegible] most appealing return of sinus rhythm wo[illegible] occur when all of the diseased left atrium h[illegible] been destroyed Nonetheless in my patient th[illegible] explanation does not fit with the fact that [illegible] waves after resumption of normal rhyth[illegible] demonstrate the same features they showed [illegible] years earlier with an obviously abnormal term[illegible] nal (left atrial) force Neither is the oppos[illegible] hypothesis tenable imputing the return of sin[illegible] rhythm to improvement of atrial tissue thro[illegible] relief of strain by lessening of wall tension esp[illegible] cially after commissurotomy In this patient t[illegible] atria look as dilated now as they were at the ti[illegible] they were fibrillating

An easy guess is that the pathogenesis of such [illegible] radical change is a very complex thing Not on[illegible] atrial myocardium is involved in the process, b[illegible] also sinus node cells, vessels nerves special int[illegible] nodal connecting fibers and surely unravel[illegible] biochemical interactions that we are hardly ab[illegible] to imagine at this time I agree with Ree e a[illegible] colleagues[9] that the pathological changes [illegible] make understandable the development [illegible] atrial fibrillation in association with chron[illegible] rheumatic heart disease but I disagree wi[illegible] them in their next statement " as well as t[illegible] spontaneous conversion to sinus rhythm [illegible] That indeed is quite a different story In fact t[illegible] spontaneous and lasting resumption of natur[illegible] sinus rhythm in atria whose components are [illegible] badly damaged is by no means understandable [illegible] the current state of our pathological and electr[illegible] physiological knowledge No doubt a lot has bee[illegible] learned about those intricated matters but the[illegible] is no doubt either that much more remains to [illegible] learned before we can clearly understand wh[illegible] and how deeply and extensively damaged atr[illegible] which have been fibrillating for years all of [illegible]

sudden are able to resume normal muscular activity under returned and lasting physiological sinus node pacing

Summary

One female patient—with slight pure mitral stenosis mild hypertension and ischemic cardio myopathy and disabling pulmonary emphyse ma—developed at 54 years of age permanent atrial fibrillation had a gratuitous mitral commissurotomy four months later sustained chronic fibrillation for 13 years then sponta neously resumed sinus node command at age 67 without any discernible reason Sinus rhythm was being maintained at follow up nine months later Her cardiac status of fair compensation under modest digitoxin and diuretic therapy has neither improved nor worsened with the return of atrial systole

The duration in this observation of permanent auricular fibrillation before spontaneous return of sinus rhythm is one of the longest ever published exceeded to the best of my knowledge only by one case of Lewis[3] and by another one of Reeve and associates[9]

Such an exceptional event points out a fasci nating enigma how can major longstanding atrial dysrhythmias (fibrillation flutter) whose causes and pathogenesis seem at least partly elucidated spontaneously disappear in atria so badly diseased? I think we must humbly confess that no satisfactory explanation is at present available for this disconcerting phenomenon

Addendum

On December 21 1978 at the time of the patient s last follow up sinus rhythm was still present—approximately 18 months after it returned Circulatory and pulmonary status were unchanged under the same treatment

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Traumatic pulmonary artery–left atrial fistula
An unusual case of cyanosis in an adult

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Communication between a pulmonary artery and the left atrium is a rare occurrence with 12 reported cases in the world s literature A recent publication has emphasized the congenital nature of this abnormality[1] This report describes a communication between the main pulmonary artery and left atrium resulting from a knife wound to the chest To our knowledge this is the first reported case of pulmonary artery–left atrial fistula of traumatic origin

Case report

A 59 year-old white male experienced an anterior myocardial infarction complicated by transient congestive heart failure five years prior to admission His hemoglobin and hematocrit were normal. He was treated with digoxin and furosemide and made an uneventful recovery One year later he discontinued all medication and returned to full employment as a machinist with no recurrence of dyspnea or other symptoms One and one half years before admission he was stabbed in the upper anterior left chest with a knife while attempting to break up a fight He entered a local hospital where a blood pressure of 90/60 mm Hg was noted. He was pale and dy pnei A one inch knife wound was present in the left second interc stal pace 3 cm from the sternal edge No murmurs were noted. A chest film revealed no change fro previous films No acute electrocardiographic changes wer noted. He received a blood transfusion and was discharged three days after admission

Thereafter he experienced gradually increasing dyspnea o exertion eventually forcing him to discontinue work as a machinist Because of persisting symptoms he was admitted to the Palo Alto Veterans Administration Hospital for evalua- tion. He complained of shortness of breath at rest and durin minimal effort but denied orthopnea, paroxysmal nocturnal dyspnea or ankle swelling Digoxin and furosemide wer reinstituted, but produced no improvement in symptoms There was no history of cyanosis or squatting in childhood or of a prior heart murmur

On admission the blood pressure was 150/80 mm Hg and the heart rate was 80 beats per minute There was cyanosis of the nail beds and mucous membranes and superficial tel- giectasis over the tip of the nose The jugular venous pressure was not increased. The chest was normal except for a 3 cm linear scar in the second intercostal space at the left sternal edge No rales or wheezes were heard on auscultation. The cardiac apical impulse was palpable in the fifth intercostal space 10 cm to the left of the midsternal line and was normal in character There was no parasternal heave The pulmonic component of the normally split second heart sound was not increased in intensity A Grade II/VI early systolic murmur and a faint Grade I/VI short early diastolic decrescendo murmur were heard at the upper left sternal border There was no clubbing and no ankle edema

The chest x ray demonstrated mild cardiomegaly with a prominent left ventricular contour but normal pulmonary vascularity The electrocardiogram demonstrated left axis deviation and evidence of an old anterior myocardial infarc- tion (Fig 1) The hemoglobin was 18 7 gm. and the hema ocrit was 55 per cent. Arterial pO_2 on room air was 50 mm. Hg and the arterial oxygen saturation was 87 per cent. The pCO_2 was 25 mm. and the pH was 7 49

Right heart catheterization was performed using a standard technique previously described. A Cournand needle was placed in the brachial artery for blood sampling and pressure recording After the completion of the resting stud [illegible]

From th [illegible] lo Alto Veterans Administration Hospital P [illegible] the D ision of Cardiology Departments of Card [illegible] d Radiology Stanford Uni ersity School of Med [illegible]

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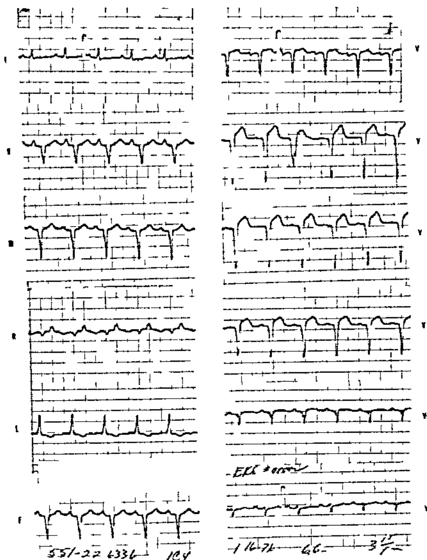


Fig 1 Electrocardiogram recorded prior to surgery Marked left axis deviation and evidence of prior anterior myocardial infarction are present One ventricular premature beat is present *(V_1)*

minutes of moderate supine exercise was performed using a calibrated cycle ergometer

Hemodynamic studies revealed a low pulmonary artery (5 mm. mean) and pulmonary capillary wedge pressure (3 mm mean) (Table I) There was a widened peripheral A V oxygen difference (6 6 ml /100 ml) and a low cardiac index (2 0 L/min /M) There was no increase in oxygen saturation from the superior vena cava to the pulmonary artery There was significant arterial desaturation (87 per cent) with a calculated right to left shunt of 0 9 L minute or 22 per cent of the systemic blood flow (assuming a pulmonary venous oxygen saturation of 95 per cent)

Angiograms of the vena cavae were normal without evidence of an anomalous communication to the left heart Injection of contrast medium into the main pulmonary artery readily demonstrated a fistulous communication between the posterior sinus of Valsalva and the left atrium through which the catheter could be maneuvered (Fig 2) Selective right and left pulmonary arteriograms were normal without evidence of pulmonary arteriovenous fistulae Left ventriculography demonstrated a moderately enlarged cavity with hypokinetic anterolateral and apical segments. Coronary arteriography revealed complete occlusion of the proximal left anterior descending artery and a small left circumflex coronary artery-left atrial fistula

Surgical closure of the pulmonary artery-left atrial fistula was recommended for the patient s severe symptomatic disability and the potential complications associated with a large right to-left shunt (paradoxical embolus, brain abscess) At operation numerous pericardial adhesions were found overlying a transverse linear depression in the anterior wall of the main pulmonary artery The pulmonary artery was entered with an anterior longitudinal incision revealing a transverse linear opening in the posterior sinus of Valsalva communicating with the left atrial chamber Lacerations of the right anterior and posterior pulmonic valve leaflets were also noted.

Table I Results of hemodynamic studies before and 4 months after closure of a pulmonary artery left atrial fistula (exercise data are indicated in parenthesis)

	Preoperative rest (exercise)		Postoperative rest (exercise)	
RA (mm Hg)	3		7	
RV S/D (mm Hg)	13/0	(24/0)	24/2	(34/8)
PA S/D (mm Hg)	13/1	(17/6)	17/8	(34/1[illegible])
PA mean (mm Hg)	5	(10)	14	(2[illegible])
PAW mean (mm Hg)	3	([illegible])	9	(1[illegible])
BA S/D (mm Hg)	170/102	(210/120)	150/91	(1[illegible]0/110)
BA mean (mm Hg)	124	(150)	115	(1[illegible]3)
SPR (dynes cm)	2750	(2160)	2550	(1660)
SVC O sat (%)	62		64	
RA O sat (%)	61		61	
PA O sat (%)	61	(44)	64	(41)
BA O sat (%)	87	(86)	96	(96)
O consumption (ml/min)	235	(580)	260	([illegible]00)
Ventilation (L/min)	9.0	(31.5)	8.0	(19.[illegible])
Systemic A-V O difference (ml/100 ml)	6.6	(10.9)	6.4	(11.0)
Systemic flow (L/min)	3.6	(5.5)	4.1	(6.4)
Pulmonary flow (L/min)	2.8	(4.6)	4.1	(6.4)
Shunt flow (L/min)	0.9	(0.9)		
R → L shunt % venous return	22	(16)		
Hgb (gms/100 ml)	19.0	(19.2)	15.0	(15.8)
Arterial pCO (mm)	35	(30)	41	(39)

Abbreviations A-V = arterial minus venous BA = brachial artery Hgb = hemoglobin O = oxygen PA = pulmonary artery PAW = pulmonary artery wedge pCO = pressure of carbon dioxide RA = right atrium R → L = right to left RV = right ventricle sat = saturation S/D = systolic/diastolic SPR = systemic peripheral resistance SVC = superior vena cava Systemic resistance is expressed as dynes/cm



Fig 2 Lateral ... showing catheter tip in pulmonary artery dur... tion A wide fistula is present (arrows) between ... ary artery and left atrium Contrast is seen ... ventricular (posteriorly) and contrast has regurg... h the pulmonic valve into the right ventricle (ant... r)

The left atrial fistula was closed with a running suture at its origin from the pulmonary artery

The small left circumflex coronary artery to left atrial fistula produced no detectable bruit or thrill and was felt to be hemodynamically insignificant

The patient made an uneventful recovery with complete resolution of his shortness of breath His systolic and diastolic murmurs at the pulmonic area increased in intensity Seven days after surgery the arterial pO on room air was 70 mm and the arterial saturation was 96 per cent The arterial pO increased to 426 mm after 10 minutes of 100 per cent oxygen breathing

Four months after surgery the patient was only minimally symptomatic and there was no cyanosis A phonocardiogram obtained at this time revealed findings consistent with pulmonic insufficiency (Fig 3) Repeat cardiac catheterization studies revealed no evidence of a residual shunt (Table I)

Discussion

The survival of patients with penetrating cardiac injuries is surprisingly common Sugg and associates[3] in reviewing a series of 459 such cases found that stab wounds generally had the best prognosis with approximately 40 per cent of the patients reaching the hospital alive The more unusual aspect of this case is the total absence of any symptoms suggestive of cardiac involveme

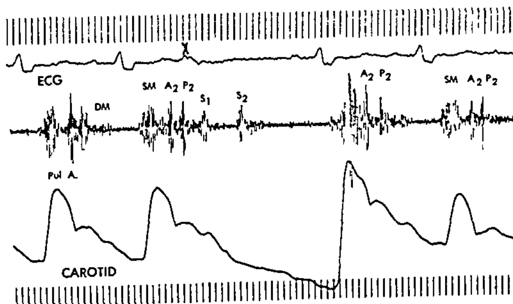


Fig 3 Phonocardiogram recorded from the third left intercostal space along the sternal edge four months after surgery One ventricular beat is present (x) A systolic murmur is present which is accentuated in the post-extrasystolic beat The second sound is widely split and the pulmonic component (P_2) is followed by a descrescendo diastolic murmur (DM) A = aortic closure sound DM = diastolic murmur ECG = electrocardiogram P = pulmonic closure sound Pul. A = pulmonary area SM = systolic murmur x = ventricular premature beat

at the time of the initial injury although this has also been commented upon in the past[4]

Previous reports have emphasized the congenital nature of pulmonary artery to left atrial communications Several anatomic variations have been described differing chiefly in the fistula s relationship to the pulmonary veins However in all earlier reports the communications have arisen from the right pulmonary artery The abnormality has been thought to originate embryologically as a pulmonary arteriovenous fistula with the venous end later being absorbed into the left atrium during normal cardiac development

Although several of the reported cases of this congenital abnormality were first recognized in adult life it is our opinion that the origin of the fistula in the present patient was traumatic for the following reasons (1) The temporal proximity of the penetrating knife wound and the onset of the patient s symptoms (2) The absence of clubbing in spite of marked cyanosis (3) The absence of polycythemia prior to injury (4) The origin of the fistula from the main pulmonary trunk rather than from the right pulmonary artery (5) The appearance of the lesion at surgery with the associated lacerations of the pulmonic valve cusps and pericardial adhesions

It is interesting to speculate that the patient s hypotension at the time of injury may have been related to a mild degree of tamponade The patient s subsequent symptoms are remarkably similar to those reported with the congenital form of pulmonary artery to left atrial communication The characteristically severe dyspnea on exertion unassociated with orthopnea ankle edema or other clinical evidence of left ventricular failure has been attributed to the arterial hypoxemia produced by the right to left shunt[1, 6]

The occlusion of the patient s left anterior descending coronary artery and the resultant anterior myocardial infarction is apparently an unrelated problem as it occurred two and one half years prior to the knife wound Nor did the resultant left ventricular contraction abnormality play a significant role in producing the patient s dyspnea as at the time of this communication he remains well and relatively asymptomatic

Hemodynamic studies revealed a low pulmonary artery pressure related to the low resistance of the shunt and pulmonary vascular bed as well as the reduced cardiac output The percentage of cardiac output shunted through the fistula did not increase during exercise so that exercise was not accompanied by a fall in arterial oxygen

saturation Similar findings have been reported in a patient with a large pulmonary arteriovenous fistula and in a patient with a congenital pulmonary–left atrial fistula[5,6] The pulmonary ventilation at rest and during exercise was markedly elevated with a decrease toward normal following closure of the fistula Values were still abnormally high following operation however The higher ventilation values prior to surgery were probably related to arterial unsaturation

The auscultatory and phonocardiographic findings following surgery were compatible with isolated pulmonary valvular insufficiency[7] These features consist of a systolic ejection murmur at the pulmonic area wide splitting of the second sound with normal order of valve closure a diastolic murmur beginning after pulmonic valve closure, and an increase in loudness with inspiration The murmur was increased in loudness following surgery probably because of the higher pulmonary artery pressure

Closure of pulmonary artery–left atrial shunts is clearly indicated not only for relief of symptoms but also to prevent paradoxical embolism or cerebral abscess[5]

Summary

Eighteen months after sustaining a stab wound to the left upper chest a 59 year old man presented with cyanosis and extertional dyspnea Arterial desaturation due to a central 22 per cent right to left shunt was present A selective pulmonary arteriogram demonstrated a fis between the main pulmonary artery and the atrium At operation the fistula was close laceration of the pulmonic valve and he pericarditis were present Marked symptom improvement followed the operation bu murmur of pulmonic valvular regurgita persisted The fistula and laceration of pulmonic valve were probably traumatic origin

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The heart as a muscle-pump system and the concept of heart failure

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Over the years few subjects have received the attention of physicians and physiologists as the description of cardiac function and in particular the evaluation of the failing heart At the turn of the century and from the laboratories of Frank and Starling emerged the view of the heart as a compression pump This concept espoused by Wiggers[3] and then by Katz[4] likened the heart to a piston-cylinder arrangement and focused on its pressure-volume relations using such displacement terms as stroke volume cardiac output and stroke work. In more recent years others such as Sonnenblick[5] Fry and colleagues[6] and Levine and Britman[7] approached this subject from a different vantage point Here the mechanical properties of cardiac muscle and in particular the behavior of its contractile element were emphasized The application of these fundamental muscle concepts to the whole heart served to broaden our view of ventricular function In the diseased heart however the confidence with which characteristics of the contractile element could be assessed was challenged The controversy focused on the muscle models and simplifying assumptions which were necessary to make such determinations and the fact that supportive experimental data were limited

In the past five years a sufficient base of information has been accumulated which permits a more detailed examination of the mechanical properties of the intact myocardium and in particular its shortening characteristics[10] [5] The evidence at hand indicates that the heart in fact may best be described as an integrated muscle pump system The purpose of this review is to elucidate the characteristics of myocardial shortening and in so doing present the heart as a muscle-pump unit That is the determinants of wall shortening regulate chamber volume displacement Finally the relevance of these behavioral characteristics of the myocardium is addressed with respect to the failing heart and the therapeutic concept of unloading

The heart as a pump

The traditional view of the heart as a pump has focused on the displacement characteristics of its ventricles That is the volume ejected per beat (i e stroke volume) or per minute (i e cardiac output) has been used to gauge the performance of the heart The comparison of stroke volume cardiac output or stroke work (obtained from the product of mean ejection pressure and stroke volume) to the filling volume of the ventricle represents one such approach which has been termed the *ventricular function curve*[8] Fig 1 represents a series of function curves As the end diastolic volume (EDV) of the normal heart is progressively raised stroke work and stroke volume increase These increments are attenuated in the failing heart where a plateau and even a decline in work may be apparent On the other hand the work performed by the heart mav be significantly augmented by such inotropic agents as norepinephrine

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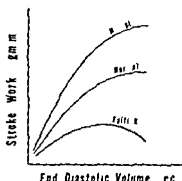


Fig 1 A series of ventricular function curves for a normal and failing heart and one in which ventricular performance and stroke work have been augmented by norepinephrine *(norepi)*

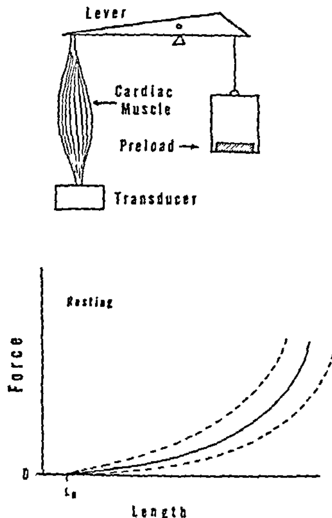


Fig 2 A [illegible] representation of an isolated papillary muscle prep[illegible]n Th[illegible] weight added to the trough prior to contraction [illegible] stretch the resting muscle to a given length [illegible] which the muscle will be stretched is dependent [illegible] of the muscle As indicated by the restin[illegible]gth relation a stiffer muscle will require a gr[illegible]ing force to achieve any given length.

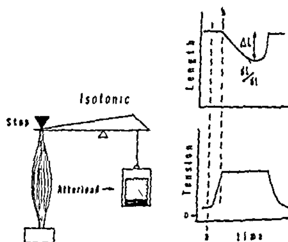


Fig 3 The addition of the mechanical stop to the lever prevents the muscle from being stretched as additional weights are added to the trough This weight which represents the grams of force which the muscle must develop and sustain in order to shorten is termed the *afterload* The extent (ΔL) and rate (dL/dt) of muscle shortening of the afterloaded isotonic contraction may be used to assess the mechanical properties of cardiac muscle

In basic terms, *work* represents the force required to move an object over a given distance In the case of the heart, work is equal to the force generated by the heart muscle times the distance the muscular wall shortens As such work is a net quantity which does not distinguish between various conditions of force and distance For example, the same work is performed moving 1,000 Gm over 3 cm as 500 Gm over 6 cm In addition work will neither reflect the efficiency nor the energy consumed by the heart in carrying these various but equivalent amounts of work. In the example cited moving 1000 Gm over 3 cm will require more oxygen (i e less efficient) than transporting the lesser weight over a greater distance

The heart as a muscle

Isolated cardiac muscle The properties of cardiac muscle were first examined some 15 years ago using isolated strips of papillary muscle[1] The concepts and terminology which arose as a result of these experiments will first be reviewed and then examined in the intact heart

Thin papillary muscles taken from the right ventricle of the cat or rabbit were studied with one end of the muscle attached to a force transducer as shown in Fig 2 and the other end secured to a level system to monitor muscle

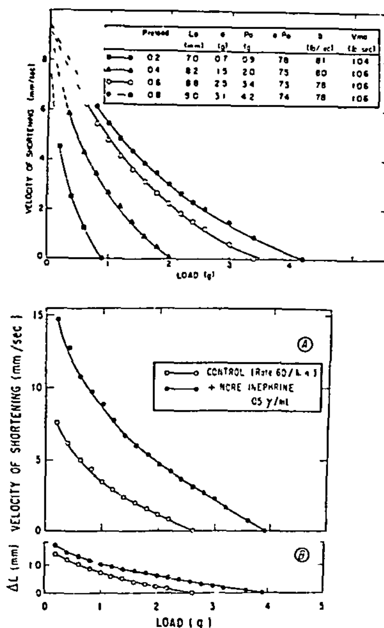


Fig 4 The response in the velocity and extent (ΔL) of shortening to variations in preload *(upper panel)* and inotropic background *(lower panel)* are presented from the data of E H Sonnenblick (Adopted with major modifications from Figs. 10 and 14 of reference 5) Note that for any given preload or contractile state an inverse relation between force and shortening is present

length By adding small weights to the trough on the opposite end of the lever the muscle is stretched and a distending force imparted to the muscle This passive force in grams which serves to impart a given stretch and length to the muscle has been termed the *preload* The extent to which the muscle will be stretched by any preload will be a function of the distensibility of the muscle That is the stiffer the muscle the greater the force required to generate any given degree of stretch or muscle length

Having now established a given length to the muscle a mechanical stop is placed at the muscle end of the lever to prevent further stretch (see Fig 3) Electrodes are used to induce a contraction of the muscle Any additional weights which are now added to the trough will be encountered by the muscle during its contraction That is a

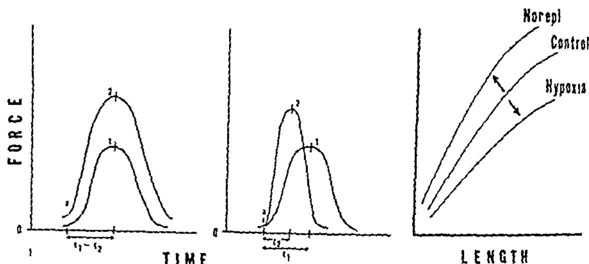


Fig 5 When the afterload is of such a magnitude that the muscle is unable to shorten an isometric (consta length) contraction results These contractions may be studied individually *(left and middle panels)* or collectively *(right panel)* to determine the influence of muscle length or contractile state on the force generating potential of the muscle

force must be generated by the muscle which is equivalent to these additional weights if the muscle is to shorten This shortening load has been termed the *afterload* During shortening these weights remain stationary in the trough and as a consequence the muscle must generate this same force throughout its contraction (i e an *isotonic* contraction) The isotonic contraction of muscle may be used to assess the properties of cardiac muscle including the extent (ΔL) and rate (dL/dt) with which it will shorten For a constant fiber length and preload illustrated in Fig 4 the extent of shortening (ΔL) declines in a linear fashion as the afterload is progressively raised[5] An inverse relation similarly exists between the velocity of shortening (dL/dt) and the load opposing that shortening The *inverse force-velocity and force-shortening relationships for a given muscle length represent a fundamental property of cardiac muscle* Another characteristic of muscle is its *length dependent property* For example at any given afterload the greater the initial length the larger ΔL and dL/dt In addition and quite independent of the influence of fiber length and afterload the extent and rate of muscle shortening are influenced by a number of diverse factors such as the chemical composition of the perfusate and the temperature of the muscle bath *This third property of cardiac muscle which is independent of loading and length has been termed the contractile state* Those factors which influence contractility in a positive or negative fashion are called *inotropic* stimuli For example when the contractile st of muscle is augmented by the addition of positive inotropic agent such as norepineph to the perfusate the extent and rate of shorten are increased for any given preload and afterloa Finally it was these observations on isotonical afterloaded contractions which served as th conceptual framework for models of cardi muscle In these models springlike and contracti elements were arranged in various combinatio and the maximal velocity of the unloade contractile element derived as an index o contractility However the dependence on presumptive arrangement of elements as well a the critical but unproven assumptions necessar to derive the maximal velocity of contracti element shortening in the intact diseased hear has tempered the enthusiasm for this type of analysis

Returning again to the isolated muscle prepa ration (Fig 5) the afterload may be further raised to a level which does not permit muscle short ening The muscle however, is able to develop this force The generation of force from a constant fiber length without muscle shorteni taking place is termed an *isometric contraction* Like the isotonic contraction the isometric contraction has also been used to describe the mechanical properties of muscle[3] For example the influence of raising the initial fiber length c the isometric force curve may be characterized by an increase in (a) the resting force, (b) the ra e of rise of force and (c) peak force without (d) a

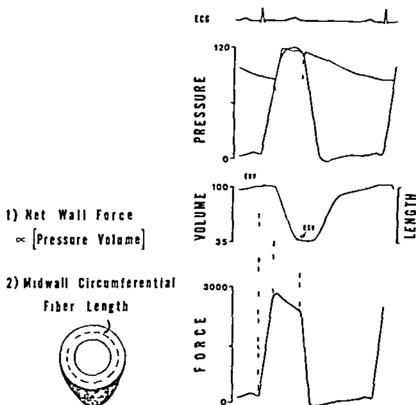


Fig 6 Net wall force is proportional to chamber pressure and dimension (i e as determined by chamber volume and configuration) The time course of ventricular and aortic pressures chamber volume fiber length, wall force and the electrocardiogram are given End-diastolic *(EDV)* and end systolic *(ESV)* volumes ha e been identified.

change in time from the onset of contraction to peak force (t = t) taking place On the other hand an increase in the contractile state of muscle which is operating from the same resting length may be identified by (a) no change in resting force (b) an increase in the initial rate of rise of force (c) an increase in peak force and (d) a decrease in the time to peak force (t < t)

In addition to considering the individual iso metric contractions their collective appraisal (the force length relationship) may be used to repre sent the properties of cardiac muscle As the muscle is stretched and its length augmented the total force generated becomes greater For any given length the force-length relation is shifted to the left with positive inotropic stimuli such as catecholamines or digitalis or downward and to the right with a negative inotropic intervention (i e hypoxia propranolol)

The intact heart The intact myocardium surrounding either ventricular chamber may be viewed as a complex arrangement of intertwining strips of muscle Moreover it is the mechanical behavior of the muscle fibers comprising the wall of the ventricle which relates to the pressure and volume events of the cardiac cycle

These pressure and volume events of cardiac contraction are an integral part of standard phys iology textbooks As shown in Fig 6 during systole the ventricle develops pressure that leads to the ejection of blood The generation of pres sure occurs as a result of the force developed by the myocardium *Chamber pressure and myocar dial force however are by no means synony mous*

Direct measurements of wall *force* indicate that force is proportional to the pressure and volume (or area) of the respective ventricular chamber If we envision the ventricle as being divided into two parts by an imaginary plane passing through a cross sectional area of its chamber and a rim of myocardium a force is created on either side of the plane This force which is equal to the pressure of blood in the chamber times the area of the chamber included in the plane tends to separate the two halves of the ventricle In accordance with Newton s law of motion this force must be counterbalanced by an

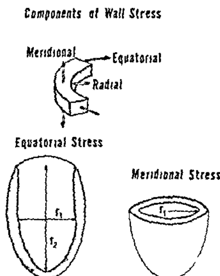


Fig 7 The components of wall stress are presented and include vectors in the equatorial meridional and radial direction The minor (r_1) and major (r_2) axes of the ventricle have also been identified See text for discussion

equal and opposite force existing in the rim of myocardium Thus myocardial *wall force in grams may be calculated as the product of chamber pressure and the cross sectional area of the chamber in the plane* Chamber configuration and volume will determine the size of this subtended area A *circumferential length* located in the midwall of the ventricle (see Fig 6) may be chosen as a simplified representative of fiber length A further description of the assumptions and rationale implicit in the derivation of these force and length calculations may be found else where[3]

The terms force tension and stress have frequently been used interchangeably in the discussion of cardiac mechanics In the strictest sense this is not correct and deserves further consideration *Net wall force* is that force which exists in the rim of myocardium subtended by the plane in question and is independent of (a) the shape area or thickness of this rim (b) the orientation of individual fibers or the distribution of forces which they generate and (c) interfascicular or shearing forces As such however it does not describe the distribution of force within the wall or consider that the wall has a finite thickness *Tension* whi h refer to the force existing in a circumferential length of myocardium included in the plane also does not relate to wall thickness *Stress* on the other hand is a term which may be used for the purpo ... s indicates the force operative within a cr ... nal area of myocardium subtended by the pl n The three major directional components of stress within t segment of myocardium shown in Fig 7 may listed as (a) an equatorial, or hoop stress wh runs in a circumferential direction (b) a mer ional stress which traverses the longitudi direction and (c) a radial stress which is direct inward toward the chamber The area of t chamber relevant to equatorial stress is th described by both the minor (r_1) and major t axes, while meridional stress is related to t smaller area given by the minor axis alone Th it is evident that for any given chamber press equatorial stress would be greater than meridional counterpart by a factor of r/r

Returning to Fig 6, the time course of mecha ical contraction may be viewed as follows At e diastole the fibers have a given stretch or leng which is determined by the given wall force T distending force which is a function of chamb pressure and myocardial compliance is analogo to the preload of the isolated muscle preparati Following depolarization the ventricle genera pressure leading to the opening of the aortic va and the ejection of blood To this point the cou of systolic pressure is related to the force dev oped by the myocardium Since the magnitude this wall force is a function of both chamb pressure and volume it is clear that the lar heart must develop more force to generate a given pressure Even though wall force is grea in the enlarged heart wall stress (i e, force j unit area of muscle) may be maintained wit the normal range by compensatory hypertrop of the myocardium[19,20] This is particular t for the patient with compensated failure T decompensated patient on the other hand m have an enlargement in chamber dimensi which is greater than the corresponding inc ment in wall thickness and hence wall stress greater than normal

During ejection the myocardium will al sustain a given force Its value is greatest near t onset of ejection however as chambe volu becomes smaller instantaneous force will decli This shortening or ejection load is analogous the afterload of the isolated muscle preparatio However unlike the constant weight which t muscle lifts after its contraction (i e an isoto load) the force on the normal ventricle has changing albeit ever declining value We ha used the term allasotonic contraction proposed by Wiggers[3] for this purpose T magnitude of this shortening load is a function

the instantaneous change in chamber size shape and pressure with the viscoelastic properties of the circulatory system dictating the time course of pressure As will be discussed in more detail subsequently these impedance characteristics of the vascular bed will influence ventricular loading [21]

It would seem prudent to define those force and length terms for the intact heart which will be used throughout this review (a) *instantaneous force* refers to that net wall force which exists at any instant during the cardiac cycle and is dependent on chamber pressure and area at that given instant The term load which has been used interchangeably throughout the text denotes this force (b) *instantaneous length* is that time varying dimension of the midwall circumferential fiber and (c) *instantaneous shortening load* (i e afterload) refers to that force which exists at any instant during ventricular ejection (i e from aortic valve opening to closure)

The maximal developed force-length relation The maximal wall force which can be developed for any degree of fiber stretch is found in the isovolumetrically beating heart This is analogous to the isometric force-length relation of isolated muscle shown in Fig 5 Under this condition the contraction of the myocardium does not result in a change in chamber volume An isovolumetric beat however does not represent an isometric contraction since the ventricle undergoes a change in shape and thus fiber length is not constant The relationship between maximal developed force and end diastole fiber length is represented in Fig 8A It is apparent that as fiber length (i e end diastolic stretch) is increased there is an associated augmentation in developed force By way of analogy we can consider the elliptical weights and muscles shown in *panel A* For the muscle length given on the left a load corresponding to the three weights could be generated but not moved Consequently the muscle will not shorten (i e an isometric contraction) On the other hand this load is the maximal force which this length of muscle can develop By stretching the muscle to a greater length indicated on the right a larger force equivalent to the six weights could be developed but again not moved The developed force length relation provides an expression of the fundamental length dependent property of cardiac muscle In this connection and unlike isolated muscle a length at which force peaks and then subsequently declines has not been demonstrated for the intact left ventricle operating within the physiological range of filling pressures (i e 1 to 25 mm Hg) [13] Thus the left ventricle normally functions on the ascending limb of its maximal force-length relation

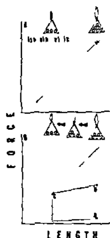


Fig 8 *A* The isovolumetric force-length relation for the intact ventricle As fiber length is raised the maximal force which may be developed becomes greater This is illustrated for the two muscle strips and the weights they are attempting to lift *B* The force-length relations for the isovolumetrically beating and ejecting ventricle are shown For the load represented at the far right the muscle is able to lift these weights and thereby shorten During shortening and while muscle length declines weights are progressively shed from the trough The muscle ceases shortening when the existing load is maximal for the given instantaneous fiber length

Variations in contractile state create nonparallel shifts in the developed force length relation positive and negative inotropic interventions raise or reduce the slope of this relation respectively For example following the administration of norepinephrine the ventricle is able to develop a greater force from any equivalent fiber length examined under control conditions That is for either muscle length shown in the insert a greater load would be generated following norepinephrine Alternatively propranolol attenuates the slope of the force-length relation and thereby reduces the maximal developed load for any given muscle length Thus the isovolumetric developed force-length relation which is contractile state dependent represents the maximal force that can be generated for any given myocardial fiber length The relevance of this relation to the ejecting heart will now be developed

The limit to wall shortening The limit to which the wall will shorten is determined by the isovolumetric force-length relation for a gi

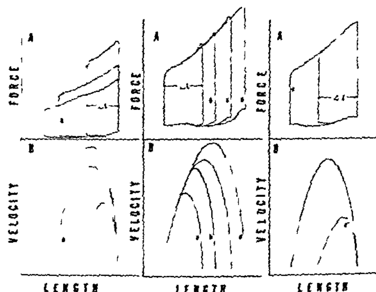


Fig 9 The trajectories of wall force the velocity of fiber shortening and fiber length are shown for the following: *(left panel)* contractions of equivalent instantaneous shortening length moving three different instantaneous shortening loads or afterloads *(middle panel)* contractions having similar trajectories of ejection force with different instantaneous shortening lengths and *(right panel)* two contractions of equivalent instantaneous length and shortening load in which myocardial contractile state has been reduced from control (beat *c* with propranolol (beat *c'*) Adopted and greatly modified from Ref. 14

contractile state That is the wall force which exists at any end systolic length equals the maximal force which that length can sustain To illustrate this further a force-length loop representing an ejecting contraction is given in *panel B* of Fig. 8 together with the corresponding isovolumetric force-length relationship From an end diastolic length denoted as point *a* the ventricle generates an isovolumic force prior to ejection Fiber shortening (i.e. ventricular ejection) commences at point *b* and continues until point *c* is reached. The course of this contraction is described as *abc* From the opening of the aortic valve to its closure the ventricle must shorten against a force whose magnitude is time varying and determined by the response in chamber pressure and dimension Note that the end systolic point *c* falls on the isovolumetric force-length line Under these conditions the ventricle may be envisioned as the muscle beginning its contraction from the fiber le[illegible] shown at the far right of *panel B* This le[illegible] equivalent to its counterpart in *panel A* [illegible] here the load at onset contraction is les[illegible] the muscle will be able to shorten As short[illegible] mences weights begin to fall from the [illegible] force is decreasing) At the intern[illegible] shortening length shown the muscle is m[illegible] maller load than that present at the onse[illegible] hts continue to fall from the trough as the [illegible] shortens Muscle shortening ceases when its given length (point *c*) can no longer move the existent load. In the example given the muscle length and load indicated at end-systole is equivalent to that shown for the isovolumetric state above

The equivalence of the end-systolic and isovolumetric force-length relations can also be shown by altering the time course of the ejection force from that shown in Fig 8B That is from the same onset ejection force (point *b*) and initial length the instantaneous force opposing shortening (i.e. the shortening load) may be varied by controlling the rate with which the weights fall from the trough For example if we induce more weights to leave the trough the muscle shortens at a much reduced load and a greater degree of shortening is permitted Alternatively retarding the rate at which the weights are shed will impose an additional load in comparison to that moved by the muscle under the conditions shown in the figure and hence shortening will be attenuated. Consequently from a given end-diastolic length three different end systolic lengths are obtained. In each case shortening ends when the ejecting force-length relation corresponds to a point on the isovolumetric force-length relation

Finally the equivalence of the isovolumetric and end systolic force-length relations has been verified for either positive (e.g. norepinephrine) or negative (e.g., propranolol) variations in

contractile state[13] Therefore regardless of its particular contractile state the ejecting ventricle contracts within the confines of its isovolumetric developed force-length relation In view of the fact that the end systolic and isovolumetric force-length relations are equivalent we[3, 11] and others[10, 23] have suggested that the end systolic relation might provide a useful clinical estimate of contractile state

Although the isovolumetric force-length relation defines the limits of shortening the extent to which the ventricle will shorten is determined by the instantaneous course of systolic force and length In contrast end systolic length is independent of initial length and onset ejection force That is the heart does not have a memory of these initial conditions Therefore end diastolic length and onset ejection force only serve to determine the starting points of the contraction

Determinants of shortening The importance of instantaneous force and length on the extent (and velocity) of midwall circumferential fiber shortening has been alluded to above To examine this further three variably loaded contractions and the respective trajectories of force velocity and length have been illustrated in *the left hand panel* of Fig 9 Each contraction originates from the same resting length The isovolumetric relation is *represented by the dotted line* In each case the extent of shortening (i e the change in length ΔL) and the velocity of shortening is determined by the *instantaneous force* opposing that shortening For beat *a* having the smallest shortening load ΔL will be greater than that found for beats *b* or *c* The velocity-length relations are indicated in *panel B* For these contractions which traverse over equivalent instantaneous ejection lengths it is clear that the *maximum and instantaneous velocity of shortening as well as the extent of shortening are determined by the instantaneous shortening load* This load dependent aspect of fiber shortening which is not represented by work represents a fundamental property of the intact ventricular myocardium

A second property of wall shortening relates to its fiber length The importance of *instantaneous length* in determining the extent and rate of shortening is illustrated in *the middle panel* of Fig 9 Here end diastolic fiber length was progressively raised by increasing end diastolic pressure from 2 mm Hg (beat *a*) to 10 mm Hg (beat *d*) For each increment or onset contraction length a

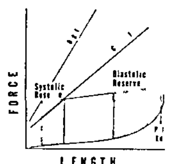


Fig 10 The concept of cardiac reserve is diagrammatically represented The reserve or increment in stroke volume which is derived as the ventricle is progressively stretched represents the heart s diastolic reserve while that increment in stroke volume which accompanies a shift in contractile state and the maximal force-length relation represents the systolic reserve

greater resting force instantaneous length maximal velocity and degree of shortening (ΔL) were observed The instantaneous shortening load however follows a common path so that each contraction terminates at a constant end systolic length Consequently the response in shortening for these beats traversing a path of equivalent instantaneous force indicates that the *rate and extent of shortening are a function of instantaneous length* This is another expression of the length-dependent (Frank Starling) property of heart muscle which is not considered in the traditional work calculation

Thus the instantaneous velocity and extent of shortening for any given contractile state is determined by both instantaneous force and length In addition to these two fundamental properties of heart muscle a third property which is independent of instantaneous force and length that is *myocardial contractile state* must also be considered The response in shortening following the pharmacological depression of the contractile state by propranolol is illustrated in *the right hand panel* of Fig 9 where control (beat *c*) and beta blockade (beat *c′*) data are given As would be predicted the end systolic force-length relation after propranolol (not shown) has been shifted to the right Hence for comparable conditions of instantaneous length and force the instantaneous velocity and extent of shortening following propranolol are reduced These alterations in shortening are analogous to those observed for the failing heart (vide infra) A positive inotropic agent such as norepinephrine or digitalis causes a shift in the opposite direction i e the end systolic force-length relation

moves to the left and a greater rate and extent of shortening are observed for any given length or load

The heart as a muscle–pump system

The concept of cardiac reserve The ability of the heart to raise its output or stroke volume has been referred to as its reserve capacity These reserves which are analogous to the inspiratory and expiratory reserves of the lung, may be visualized as follows (see Fig 10) the heart s *diastolic reserve* reflects the increment in shortening which is possible when the ventricle draws on its fiber length capabilities (i e chamber dilatation) By raising diastolic stretch into the cross hatched area designated diastolic reserve in Fig 10, stroke volume is raised The ventricle for example may draw on this reserve compensatorily during increments in arterial pressure or venous return or following a compromise in myocardial contractility Its limits are determined physiologically by the levels of accompanying pulmonary hydrostatic pressure and edema formation

The *systolic reserve* is brought to bear during positive shifts in contractile state That is a contraction which is induced to shorten beyond its present end systolic volume as would occur following the administration of digitalis will utilize this reserve End diastolic volume need not be influenced The maximal force–length relation on the other hand is shifted to the left The extent of this shift which again determines the new limits to this augmented shortening is dependent on (a) the strength of the applied stimulus (i e the amount of digitalis given or the use of several positive inotropic interventions in combination) and (b) the state of the myocardium (i e a failing heart responding to a lesser degree than a normal ventricle) A severely compromised heart in which the isovolumetric force–length relation has been greatly reduced may in fact be refractory to such agents

As a pump the ventricle generates pressure and displaces volume It should now be apparent that these properties of the heart as a pump may be expressed in terms of the development of muscle force and fiber shortening respectively In this context the heart s pumping characteristics are an expression of the behavior of the muscle fibers which comprise its wall

Commencing with the opening of the aortic valve the myocardium must accelerate the column of blood, with its given inertia into the vascular system Up to this point in their contraction the fibers have already been loaded by a force proportional to chamber pressure and dimension Under normal circumstances the load imposed by the outflow tract and semilunar valve will be negligible The force on the contracting fibers, however is influenced by the resistance and capacitance elements of the vasculature The force resulting from the resistive component is a function of the velocity of fiber shortening (i.e., ejection rate) whereas that force attributable to the capacitive portion is related to the extent of fiber shortening or the volume ejected.

This heart–vessel interaction may also be viewed as a feedback control of myocardial contraction [21] For example an increment in stroke volume (and ejection rate) leads to an increase in aortic impedance (decreased capacitance) and subsequently in wall force As a result of this increased load subsequent contractions have an attenuated stroke volume Contrariwise if an increment in aortic impedance were the initial event the accompanying reduction in stroke volume should lead to both a greater end systolic and end diastolic chamber volume. As a consequence of this increase in fiber length stroke volume would be restored to original level In the failing heart in which systemic perfusion is not maintained at adequate levels peripheral resistance is raised to preserve arterial pressure. The pharmacological reduction of this increased resistance using vasodilators has been utilized to unload such a heart (vide infra) This coupling between the heart and vascular bed necessitates that cardiac fibers be able to react not only to beat to beat variations in filling volume and arterial impedance but also that they adjust instantaneously to differences in length and load. That this is indeed possible has been presented in the previous section

In addition to the influence of pressure on ventricular loading the change in ventricular dimension represents an important determinant of shortening load The alteration in dimension for any given load will be a function of the geometrical configuration of the chamber as well as myocardial contractile state In the normal heart the reduction in radius throughout ejection

permits wall force to decline despite the fact that chamber pressure increases Burch and colleagues have pointed out some years ago that as the heart enlarges it loses this advantage For example the extent of shortening by fibers compromising the wall of a large spherical ventricle is less than that associated with an equivalent stroke volume from a smaller chamber Thus the marked abbreviation in shortening in the enlarged and failing ventricle will contribute significantly to instantaneous load for any given condition of arterial pressure This important aspect of the failing heart will be discussed further below

According to the traditional pump concept the performance of the ventricle may be gauged from the stroke volume to end diastolic volume relationship Stroke volume may be raised by the augmentation in filling volume (Frank Starling response) or myocardial contractile state (e g catecholamines or digitalis) Stroke volume however is also dependent on arterial pressure [11] Elevations in systolic pressure and concomitantly in wall force serve to reduce the ejected fraction or stroke volume from any given diastolic volume Alternatively a reduction in impedance as with aortic or mitral regurgitation or an arteriovenous shunt allows for a greater ventricular emptying

The product of stroke volume and aortic pressure which approximates stroke work has also been utilized to assess pump function As mentioned previously the relationship of work to end-diastolic volume (or end diastolic pressure) has been termed the *ventricular function curve* Now that the muscular properties of the myocardium are understood the origins of this relation which are critical to understanding its meaning may be elucidated For any given contractile state the extent to which a fiber will shorten will depend on its instantaneous length and force Taking the instantaneous force trajectory shown in *the middle panel* of Fig 9 for example increments in end diastolic and instantaneous length result in progressive elevations in stroke volume (or shortening) thereby describing the shortening-length relation A number of such linear shortening-length relationships derived for a series of force trajectories (F) where $F_1 < F_2 < \quad < F$ have been given in Fig 11 The slope of each shortening-length relation is

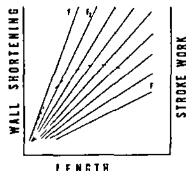


Fig 11 The traditional ventricular function curve is derived from the shortening length relations obtained for a series of instantaneous force trajectories where F < F < < F

reduced as the absolute level of the force trajectory is increased However in the intact animal or in man it is obviously not possible to maintain these rigidly controlled conditions of loading when deriving a function curve For example when the circulating volume is expanded using dextran both the intracardiac and intravascular (capacitance) space are expanded Consequently arterial pressure chamber dimension and instantaneous force increase on a continuous basis The resultant work to diastolic volume (or fiber length) relation thereby traverses these shortening-length relations as indicated by *the dotted line* in Fig 11 Alterations in myocardial contractile state for any given heart or differences in contractility between hearts produce a series or family of function curves Despite these limitations the absolute level of stroke work has in fact been found to provide a useful clinical estimate of the degree of ventricular dysfunction following acute myocardial infarction

The failing heart

As we have used the term here heart failure refers specifically to a compromised contractile state of the left ventricle which is accompanied by an inadequate forward flow to accommodate the needs of the peripheral circulation Because ventricular emptying is less signs and symptoms of pulmonary venous hypertension may also be present The reduction in contractile state and the decreased slope of the isovolumetric force-length relation accounts for the decline in both the extent and rate of fiber shortening for any condition of length or load The force-length loop given in Fig 9 for propranolol would be illustrative of this circumstance This attenuation

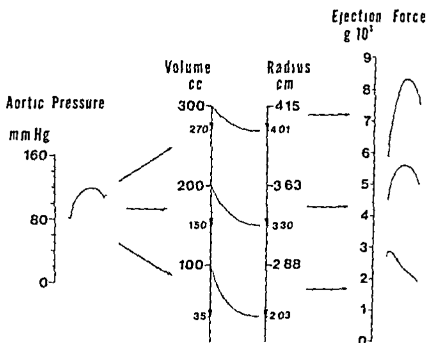


Fig 12 The response in ventricular dimension represents an important determinant of instantaneous shortening load or afterload In the normal heart the reduction in chamber radius permits wall force to decline during ejection In the failing ventricle enlarged to two and three times its normal size it lo es this advantage and an abnormal load must be sustained by the shortening fibers

in shortening implies that the slope of the short ening-length relation is also reduced Translated into terms of the heart s function as a pump stroke volume ejection fraction and ejection rate will be reduced

The depression in the maximal force–length relation itself represents a reduction in the heart s systolic reserve In other words the ability of positive inotropic agents such as digitalis to shift this relation to the left and permit greater short ening becomes attenuated In addition the inher ent toxicity and rate of renal clearance of digitalis limits the extent of its daily administration A critical reduction in systolic reserve exists when the failing ventricle becomes refractory to such agents It is here that increments in shortening may only be achieved by manipulating instanta neous force (i e the concept of unloading) such as with vasodilators Each decrement in the developed force–length relation will also atten uate the ability of the heart s diastolic reserve to restore stroke volume That is the increment in shortening which is possible through chamber dilatation (i e greater fiber length) becomes less as the limits to shortening are reduced

In this connection one other point deserves comment The reduction in chamber dimension or radius during ejection is abbreviated in the enlarged failing ventricle That is the change in ventricular size from end diastole to end ejection is less than under normal conditions This circum stance may be accounted for by (a) the reduced stroke volume of the failing heart and (b) the fact that its end diastolic chamber size is enlarged In this connection recall that for any given stroke volume the extent of shortening of fibers encom passing a large ventricle is less than that of a smaller chamber When wall motion becomes severely attenuated creating an essentially invar iant chamber dimension the absolute level of systolic force remains high (i e essentially unchanged from its onset value or even increasing throughout the ejection period) This sustained shortening load further decreases the degree of wall shortening As shown in Fig 12 the enlarge ment of the ventricular chamber (two and three fold normal size) and a reduction in contractile state both account for the abnormally high and sustained shortening load Reducing chamber size and thereby instantaneous force in such a heart with a diuretic by venesection or vasodilator permits an increase in shortening without influencing contractility According to the tradi tional viewpoint this increment in stroke volume represents an ascent from a depressed position on the ventricular function curve

The concept of unloading Positive inotropic agents such as digitalis aimed at improving contractile state forward flow and the symptoms of pulmonary venous hypertension have long been the mainstay for treating the compromised ventricle *In the chronically failing enlarged* heart characterized by a marked reduction in its maximal force-length relation (i e a limited systolic reserve) it may no longer be possible to augment shortening by such measures (i e refractory failure) Alternatively in the acutely ischemic failing heart these agents unfavorably augment metabolic demand and thereby may increase infarct size Under either circumstance it is necessary to work within the heart s given contractile state while providing for conditions which favor a greater degree of fiber shortening This is accomplished by reducing instantaneous shortening load or more specifically by lowering the pressure and radius variables of systolic wall force Toward this end a number of vasodilators have received much recent attention [7,23] The cardio circulatory effects of these agents however differ depending on their relative influence on the systemic resistance and venous capacitance vessels Despite these relative differences chamber volume and pressure are both perturbed throughout the cardiac cycle following the administration of these agents Hence instantaneous load will be altered Therefore it is not appropriate to consider that any particular vasodilator will exclusively influence end diastolic force or shortening load This is not meant to imply however that there would not necessarily be a predominant effect as in the case of hydralazine where its pharmacological action is directed almost entirely at arterial smooth muscle and thereby shortening load

The response of any ventricle to these agents will depend on its size distensibility and contractile state These factors plus the cardiocirculatory effects of the individual vasodilators deserve consideration when selecting among these agents for any given patient For example in the enlarged failing ventricle with high filling pressure nitroprusside and phentolamine provide a significant reduction in systemic arterial and ventricular end diastolic pressures while stroke volume (i e wall shortening) is raised In these hearts the increment in fiber shortening induced by the reduction in instantaneous systolic force is greater than the moderate counteracting reduction in instantaneous fiber length However when the reduction in filling pressure (i e to levels < 10 mm Hg) and length is marked stroke volume declines or does not change Here the attenuation in fiber length or diastolic reserve *predominates and outweighs the reduction in* instantaneous force In similar fashion stroke volume could be expected to decline when filling pressure is reduced in a noncompliant ventricle However under these conditions the extent of venodilation required to significantly reduce pressure is much less

The appropriate selection of a particular vasodilator should therefore be based on filling pressure ventricular size and cardiac output Obviously the degree of urgency and the given clinical state of the patient in heart failure as well as the route of vasodilator administration will also dictate the choice of agent For the enlarged ventricle with elevated filling pressure (> 15 mm Hg) and an abnormally high shortening load it would be preferable to choose an agent(s) which would significantly reduce both chamber dimension and systolic pressure Nitroprusside or the combination of hydralazine and isosorbide dinitrate would appear appropriate for this purpose The noncompliant ventricle would seemingly derive a greater benefit from hydralazine since the reduction in filling pressure will be less pronounced

Conclusion

The heart functions as an integrated muscle-pump system so that the determinants of myocardial fiber shortening regulate the volume displaced from the chamber In this review we have attempted to unite these two concepts of performance by examining the ventricle as a pump as well as the behavioral characteristics of its circumferentially oriented fibers. The isovolumetric force-length relation which depends on the contractile state of these fibers describes the maximal force attainable for any degree of fiber stretch It further establishes the limits to fiber shortening During ejection the extent and rate of fiber shortening are determined by the instantaneous trajectories of wall force (i e a function of chamber pressure and dimension) and fiber length as well as by the contractile state of the myocardium These properties of the myocardium may be utilized to describe the heart as a pump including the derivation of the ventricular

function curve Finally the relevance of these relationships in characterizing the failing heart is emphasized Specifically the attenuation in slope of the maximal force-length relation and the sustained shortening load of the enlarged chamber account for the reduced output of the compromised ventricle Vasodilators may be used to lower this abnormal shortening load thereby unloading the failing ventricle and permitting greater fiber shortening and forward flow

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Fundamentals of clinical cardiology

The pathology of cardiomyopathies A critical analysis

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Investigative work and case reports on cardio myopathies have been the subject of many communications in recent years but even today confusion as to which cardiac condition should be included or excluded under this term still exists To simplify and clarify matters it has been proposed that *Cardiomyopathy* should be re stricted to the group previously known as pri mary cardiomyopathy and that secondary cardiomyopathy should be replaced by *Specific Heart Muscle Disease* into which metabolic general systemic diseases heredo familial neuro muscular disorders sensitivity and toxic reaction and possibly myocarditis should be included

Over the years lengthy and cumbersome defini tions have been modified to Heart muscle disease of unknown causes This definition has the advantage of being short and to the point The classification based on hemodynamic and structural changes will be employed

Classification of cardiomyopathies

Three major groups are recognized

1 Congestive (dilated)
2 Hypertrophic (with or without obstruction)
3 Obliterative/restrictive

This analysis will concentrate on the structural changes

Congestive (dilated) cardiomyopathy At ne cropsy the overweight hearts show severe dilata tion of all cardiac chambers and pale and flabby myocardium The degree of hypertrophy may be masked by the dilatation resulting in normal values of cardiac wall measurements Foci of fibrous replacement limited to the inner layer of the myocardium may be found particularly in long standing cases The endocardium is usually thickened and in 60 per cent of cases thrombus may be superimposed No organic abnormalities are found in the heart (or elsewhere in the body) which could have resulted in heart failure but functional changes such as thickening of the valve leaflets due to existing insufficiency may be found With rare exception the coronary arteries are normal [9]

Histology No specific features are found and the myocardial fibers are predominantly regular ly arranged Their diameter is usually normal (5 to 12 μm) but nuclear changes of hypertrophy may be striking This discrepancy is due to the attenuation of the fibers [1] Foci of irregular arrangement may occasionally be found

The increase in fibrous tissue may take the form of an increase in the interstitial collagen component or replacement of myocardial fibers The small vessels are usually normal but in the fibrous areas the vessels may occasionally show intimal thickening It is highly likely that the vascular abnormalities are secondary in nature The endocardium shows hypertrophy of the smooth muscle reflecting long st nding dilata tion

Histochemistry The changes vary according to how long the heart failure (i e dilatation) has been present As postmortem examinations usual ly preclude this type of investigation much infor mation has been obtained from fresh endomyo cardial tissue obtained by Bioptome [1] An increase normal amounts or a decrease in substances such as glycogen and succinic dehy drogenase may therefore be found [1]

Electronmicroscopy The changes of hypertro

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phy characterized by an increase in mitochondria, showing variability in size and shape an increased number of ribosomes convolutions of the nuclear membranes and varying degrees of glycogen accumulation are found Changes of degeneration may also be found[11] The myofibrils are usually regularly arranged but irregular arrangement may be found, as encountered in hypertrophy in general[17]

Conditions mimicking congestive cardiomyopathy

ALCOHOLIC HEART MUSCLE DISEASE Experimental and human investigations have shown that alcohol has a deleterious effect on the myocardium[1] Though characteristic features have been described for this type of heart muscle disease,[1] they may be found in congestive cardiomyopathy and therefore distinction is usually impossible It may be that alcohol in some patients may be contributory to congestive cardiomyopathy

Heart failure associated with *pregnancy* or the *puerperium* can also not be distinguished pathologically from patients with congestive cardiomyopathy

ISOLATED ENDOMYOCARDIAL FIBROELASTOSIS IN THE NEWBORN AND YOUNG CHILDREN is difficult to classify but should be suspected if congestive cardiac failure occurs in babies under six months of age Clinical and pathological distinctions exist At histological examination the thick endocardium shows regular arrangement of elastic fibers

Etiological suggestions for congestive cardiomyopathy The etiology of the congestive (dilated) form of cardiomyopathy is by definition unknown Suggestions of possible etiologies have included a decrease in succinic dehydrogenase (it is likely that these changes occur secondary to heart failure) and abnormalities of small vessels Whereas in isolated fibrous foci changes in small vessels may occur in the vast majority of cases the arterioles are consistently normal An analogy may be drawn from the suggested small vessel etiology of heart disease in Friedreich's ataxia Only in 9 per cent of vessels were changes of sufficient magnitude found and it was therefore considered unlikely that diffuse myocardial fibrosis in the myocardium was the result of small vessel disease [illegible] that condition A possible causative infecti[illegible] [illegible]ent has been proposed but possible misinter[illegible]ation of these findings has been advanced[16] An autoimmune etiology has been forwarded[1] immunologic changes have been found[21] Hypertensive disease in disguise has also been proposed and has been substantiated in some cases[1] A possible viral etiology was suggested in 1967[3] More recently, a significantly higher titer for Coxsackie B virus has been found in some patients with congestive cardiomyopathy compared to the general population[1]

No definite proof for these various etiological suggestions exists It may well be that congestive cardiomyopathy has a multifactorial etiology

Hypertrophic cardiomyopathy

A With obstruction The clinical and pathologic characteristics of this condition are well established Structural changes have been delineated from cases observed at necropsy[1] and from surgical material where removal of tissue formed part of the operation[1] Though hypertrophy of all chambers is present, the asymmetric hypertrophy of the interventricular septum is striking Displacement of the anterior papillary muscle and characteristic deformities of the ventricular cavity are usually sufficiently characteristic to permit the diagnosis to be made Endocardial thickening particularly beneath the aortic valve is often found as well as jet lesions on the under surface of the anterior mitral valve leaflet The coronary arteries are usually normal

Histology The histologic features have been semi quantitatively analyzed[1] and consist of short runs of severely hypertrophied fibers interrupted by connective tissue large bizarre [illegible] fibrosis degenerating muscle fibers with disappearing myofibrils resulting in a clear perinuclear area and disorganized whorling of muscle fibers The small vessels are usually completely normal

Histochemistry This type of analysis has been extensively undertaken[1] An increase in glycogen is striking and is diagnostically helpful This immense glycogen accumulation in conjunction with the histologic changes permits a diagnosis with a high degree of accuracy[16]

Electronmicroscopy This reflects the changes seen at the light microscopic level consisting of disarray of myocardial fibrils which seemingly run in all directions Increased cellular branching and extensive side to side intercellular junction occur Severe convolutions of the nuclear membrane focal immense accumulations of mito-

chondria and glycogen are often seen[16] These changes may however also be seen in hypertrophy due to known causes[11, 1, 1] and in congestive cardiomyopathy[13, 17]

Reliability of macroscopic histologic as well as electronmicroscopic characteristics have recently been questioned as to whether they permit a firm diagnosis of hypertrophic cardiomyopathy to be made Interventricular septal thickening has been found in association with congenital and other heart disease as well as in fetal hearts [43] Of eight patients with interventricular septal thickening analyzed only two showed histologic features suggestive of hypertrophic cardiomyopathy[4] Resolution of disproportionate ventricular septal thickening has been shown to occur [3] Thus asymmetric hypertrophy alone particularly when associated with other disease processes should be viewed with caution and as in echocardiographic appearances it is the *combination* of changes that permit a diagnosis rather than an isolated feature[3]

Doubt as to the histologic characteristics has been expressed particularly regarding the disarray of myocardial fibers[4, 4] These are often encountered in hypertrophy occurring as a result of congenital heart disease and other cardiac conditions and even in normal hearts There is no doubt that irregular arrangement of hypertrophied myocardial fibers can occur in the various conditions particularly at the junction of the interventricular septum and the free ventricular walls Disarray by itself does however not constitute hypertrophic cardiomyopathy as was already emphasized in 1971 The changes are usually more severe in hypertrophic cardiomyopathy Quite apart from the severe degrees of disarray it is the changes of extreme hypertrophy the bizarre shaped nuclei surrounded by a clear zone whorl formation and the enormous accumulation of glycogen which characterize hypertrophic cardiomyopathy Regarding electronmicroscopic examination increased cellular branching and extensive side to side intercellular junctions were considered unique for hypertrophic cardiomyopathy Overlap of these changes in hypertrophic cardiomyopathy compared with ordinary hypertrophy has been reported [1, 1, 41] Indeed more extensive changes were found in acquired heart disease than in hypertrophic cardiomyopathy There can be no doubt that macroscopic appearances together with histologic and histochemical examination permit a firm diagnosis of hypertrophic cardiomyopathy and additional confirmation may be obtained from electronmicroscopic examination Any of these features in isolation do not constitute a diagnosis of hypertrophic cardiomyopathy nor can one conclude that a common underlying mechanism of these changes exists Hypertrophic cardiomyopathy may however occur in association with other conditions including lentigenosis coronary arterial disease[5] Turner s syndrome[31] hyperthyroidism isolated dextroversion[31] Friedreich s ataxia [13] and also possibly pulmonary arterial malformation

B *Without obstruction* In these patients similar changes to those described above are found including asymmetric hypertrophy of the interventricular septum which despite the rare occurrence of preterminal heart failure usually but not invariably persists It has been believed that the distribution between the two clinical conditions varies In hypertrophic cardiomyopathy with obstruction the changes were confined to the asymmetrically thickened interventricular septum whereas in cases without obstruction foci of these changes were irregularly distributed throughout the ventricular walls More recently two children have been documented in which clinical evidence of obstruction existed but at postmortem the distribution of non obstruction was found The authors stressed that morphological criteria for obstruction and non obstruction are not always reliable Fiber disarray in the septum and free ventricular walls have also been found by other investigators in both the obstructive and non obstructive forms

VARIANTS OF HYPERTROPHIC OBSTRUCTION CARDIOMYOPATHY Mid ventricular obstruction has been described as well as asymmetric apical hypertrophy[51] which could possibly be included under this heading

Although hypertrophic cardiomyopathy has received great attention since the original clinical observation in 1957 and the pathological description in 1958 cases have been described almost 90 years before this [1] An embryonic growth disturbance as an etiologic possibility was suggested in 1907[6] Hamartoma[38] increased noradrenalin in the region of the asymmetric hypertrophy[1] a primary disorder of muscle metabolism [5] and a myopathic disorder accompanying skeletal muscle changes have also been

suggested as well as hypertension[67] A genetic basis of either a mendelian dominant or autosomal dominant trait with almost complete penetrance has been established[6] ' A relationship with catecholamines has been raised [0] and small vessel disease as a possible cause has also been proposed ' Abnormal contractions occurring towards the end of systolic isometric contraction interfering with normal muscle fiber alignment had been suggested either as a result of cavity obliteration and/or because of a catenoid shape of the septum [3] (convex to the left from apex to base concave to left in the horizontal plane) Isometric contraction in the absence of cavity obstruction has been suggested [4]

Obliterative/restrictive cardiomyopathy This final group of cardiomyopathies will be described together because no distinguishing structural changes *in these conditions exist Under this* heading endomyocardial fibrosis and Loffler s endocarditis parietalis fibroplastica (Loffler s endocarditis) are included

Endomyocardial fibrosis Morphological examination shows striking endocardial changes [4] Though the distribution of endocardial changes may vary in the affected areas the endocardium is several millimeters thick (normal up to 20 μm thick in the left ventricular outflow tract) Not infrequently when the left ventricle is involved the posterior mitral valve leaflet and posterior papillary muscle apex and part of the interventricular septum are affected The endocardial thickening usually ends abruptly in a thick rolled edge

Histology The thick endocardium is arranged in zones Superficially thrombus is frequently found followed by a zone of hyaline collagen tissue in which foci of calcification may be present The next zone consists of fibrous tissue and the deepest zone consists of loosely arranged connective tissue in which dilated blood vessels varying degrees of an inflammatory infiltrate as well as eosinophils may be found From this layer fine strands or septa extend into the underlying myocardium confined however to the inner third of the cardiac wall

Loffler s endocarditis [80] [4] This condition resembles endomyocardial fibrosis though large thrombi may fill the ventricular cavities Analysis of previously published cases suggested that Loffler s endocarditis and endomyocardial fibrosis belonged to the same disease spectrum the origin of which could be traced back to the presence of eosinophils in the myocardium The cause of the eosinophilia might either be idiopathic or reactive such as occurring in conjunction with anti tuberculous treatment asthma and carcinoma or might be leukemic in origin

Progressive histologic stages have been established which vary with the length of history The first stage the necrotic stage (average duration of history 5 5 weeks) consists of eosinophilic myocarditis and necrotic foci which eventually are destined to give rise to the small septa noted above The second the thrombotic stage (average duration of history 10 months) shows some endocardial thickening and severe thrombus superimposition The last stage the fibrotic stage (average duration of history 24 5 months) shows *identical features to those* described under endomyocardial fibrosis

Under the term Loffler s endocarditis Belgian and Nigerian workers reported cases from Nigeria and the then Belgian Congo and have demonstrated that eosinophils may be present at some stage during the disease process Endomyocardial fibrosis with eosinophilia has been noted in three cases from Venezuela[8] Cases showing the changes of endomyocardial fibrosis occurring in Denmark[8] and in Switzerland[9] have also been documented Therefore the assumption that endomyocardial fibrosis is confined to the tropical and subtropical regions and Loffler s endocarditis is confined to the temperate zones does not seem to apply

Evidence exists that large proportion of circulating eosinophils are abnormal in patients with Loffler s endocarditis and show the characteristics of mature stimulated cells[4] Work is in progress to investigate extensively the role th eosinophils may play in this type of cardiomyopathy Apart from the possible causal role of eosinophils other etiological suggestions have included lymphatic obstruction high plantain consumption filariasis and a hypersensitivity response to streptococci ' Infective toxic nutritional and an abnormal immunological reaction have been suggested as well as geographic and environmental influences

Value of bioptome investigation From the description of the morphologic changes it will be evident that distinguishing features between the three major groups of cardiomyopathy exi

Furthermore morphologic examination has provided an understanding of many clinical features but with the exception of eosinophils in obliterative/restrictive cardiomyopathy has unfortunately not contributed to establishing possible underlying causes When the bioptome an instrument consisting essentially of catheter with an operating handle at one end and a cutting device at the other was first described[* 5] fresh endomyocardial tissue could be safely recovered by this technique By means of this instrument or adaptations of other instruments[96 *] the technique is being used with increasing frequency[99] The procedure is safe in experienced hands but should be confined to a few specialized centers particularly to those where surgery is available Investigations should be undertaken when the diagnosis is seriously in doubt and where it is likely that examination might provide a helpful answer[100] Although no specific changes are present in cases of congestive cardiomyopathy the pathological diagnosis is made in conjunction with the clinical diagnosis both being made by exclusion

Morphologically myocarditis or infiltrative disease must be excluded before the clinical diagnosis of congestive cardiomyopathy can be confirmed[1]

The value in differentiating rheumatic heart disease from congestive cardiomyopathy in Uganda has been stressed

Interpretation of structural changes has not been confined to diagnostic aspects but has been extended to include morphometry and has also been related to clinical findings such as length of history ejection fraction left ventricular end diastolic pressure and other hemodynamic parameters[1 3] Examination of the biopsy material has provided the means to establish an extensive classification of cardiomyopathies[96] Myocardial biopsies have also been used to establish prognosis in patients with congestive cardiomyopathy

Great activity in a search for possible etiologic agents is in progress Biochemical analyses are being undertaken on the fresh endomyocardial tissue obtained by bioptome Immunological work is in progress and viral studies are also being undertaken

For all these various investigations morphologic examination provides insight into the distribution of the various components of the myocardium which is essential for correct interpretation of the results of biochemical and immunologic analyses Continuation and expansion of these investigations is essential concentrating in particular on the earliest stages of the disease process It is hoped that by these means many of the problems will be solved among which the natural history of congestive cardiomyopathy the mechanism of fiber disarray in hypertrophic cardiomyopathy and the role of eosinophils in the obliterative/restrictive type of cardiomyopathy are high on the list

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Clinical pharmacology of the new beta-adrenergic blocking drugs Part 5 Pindolol (LB 46) therapy for supraventricular arrhythmia a viable alternative to propranolol in patients with bronchospasm*

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Since their introduction as antiarrhythmic agents beta adrenoceptor blocking drugs have proved to be effective and safe against supra ventricular and ventricular arrhythmias when administered intravenously and orally β blockade appears to be the main antiarrhythmic mechanism and it is reasonable to expect that all β adrenoceptor antagonists will have comparable antiarrhythmic efficacy for a given degree of β blockade To date an undisputed superiority of one β blocking drug over another in the treatment of arrhythmias has not been clearly demonstrated Any differences in their over all clinical benefits must therefore be assumed to be related to variations in their associated pharmacological properties (cardioselectivity intrinsic sympathomimetic activity)

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Propranolol blocks both cardiac (beta$_1$) and smooth muscle (beta) receptors and can potentially precipitate bronchoconstriction in certain patients Some beta receptor blocking drugs have a degree of selectivity for beta$_1$ receptors as opposed to beta receptors and these drugs are less likely to provoke asthma although the relative risk is hard to quantify and is almost certainly dependent on the dose used Thus low doses of a given agent might produce appreciable cardiac beta receptor blockade with only a minor degree of blockade of smooth muscle receptors however in high doses selectivity is lost

Other beta receptor blocking drugs have a high degree of intrinsic sympathomimetic activity and this has been claimed to lessen the risk of bronchospasm If the newer beta adrenoceptor blocking drugs are to be useful they should be able with their other pharmacological properties to substitute for propranolol in situations where bronchospasm (and myocardial depression) are potential problems One of these newer agents pindolol (LB-46) is a non cardioselective β blocker with the most intrinsic sympathomimetic activity of the β blocking agents (direct agonist activity) currently available for clinical use

The present study reports the efficacy of pindolol in the treatment of supraventricular arrhyth

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Table I Summary of the effects of intravenous pindolol (LB 46) in the acute management of patients with supraventricular tachycardia

	No of patients	*Ventricular rate reduced to 100 beats/min with or without return to sinus rhythm*	*Return to sinus rhythm*	*No response*
Paroxysmal supraventricular tachycardia	7	6	6	1
Atrial fibrillation	6	6	3	0
Atrial flutter	2	1	1	1
Junctional tachycardia	2	2	2	0
Multifocal atrial tachycardia	1	1	1	0

Table II Summary of the effects of oral pindolol (LB-46) in the long term management of patients with supraventricular tachycardia

	No of patients	*Long term efficacy (rate slowing or maintenance in NSR)*	*Frequent recurrence of arrhythmia*
Paroxysmal supraventricular tachycardia	6	4	2
Atrial fibrillation	6	5	1
Atrial flutter	1	1	0
Junctional tachycardia	2	2	0
Multifocal atrial tachycardia	1	0	1

Godart Pulmotest Apparatus Per cent differences in mean FEV_1 /VC for the different treatment intervals were tested for significance by the one sample t test

Results

Intravenous studies All 18 patients with paroxysmal supraventricular arrhythmia failed to respond to intravenous placebo and received intravenous pindolol (0 4 to 1 4 mg)

Six of seven patients with paroxysmal supraventricular tachycardia converted to normal sinus rhythm In the six patients with atrial fibrillation three converted to normal sinus rhythm and three demonstrated only ventricular rate slowing Of the two patients with atrial flutter one converted to normal sinus rhythm and one had no response Both patients with junctional tachycardia converted to normal sinus rhythm as did the one patient with multifocal atrial tachycardia (Table I)

Untoward bradyarrhythmias were not observed in any patients Seventeen of the 18 patients noted no subjective aggravation of their bronchospastic disease one patient reported a worsening of his asthma No patient developed clinical evidence of congestive heart failure

Oral studies The 16 patients who responded to intravenous pindolol therapy received oral therapy (2 5 mg to 10 mg every 6 hours) for long term maintenance Of the six patients with paroxysmal supraventricular tachycardia treated with oral pindolol four were maintained in normal sinus rhythm (one of these responded well after a second intravenous pindolol intervention) Two patients with paroxysmal supraventricular tachycardia had frequent recurrence of the arrhythmia and were considered non responders to oral pindolol Of the six patients with atrial fibrillation five continued to respond (with either continued ventricular rate slowing or maintenance in normal sinus rhythm) and one patient reverted to atrial fibrillation with a rapid ventricular response The patient with multifocal atrial tachycardia could not be maintained in normal sinus rhythm with oral pindolol The two patients with junctional tachycardia and the one with atrial flutter remained in normal sinus rhythm with oral pindolol (Table II)

Of the 16 patients receiving oral pindolol therapy 14 noted no aggravation of their bronchospastic disease one felt improved and one experienced an exacerbation Two patients developed a self limited morbilliform erythematous rash which did not warrant cessation of drug therapy One patient complained of transient dizziness

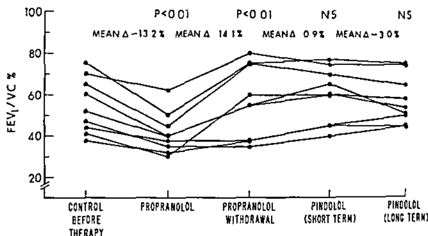


Fig 1 Effects of propranolol and pindolol on FEV /VC in patients with histories of bronchospastic disease aggravated by propranolol There was a significant deterioration of FEV /VC with propranolol compared to a non treatment period an effect which was completely reversed by drug withdrawal No significant deterioration in FEV /VC was observed with pindolol treatment in either intravenous or oral form compared to the non treatment period

without hypotension or bradycardia There was no subjective or clinical evidence of congestive heart failure in any patient

Pulmonary function studies (Fig 1) Nine of the patients with propranolol induced broncho spasm had spirometric measurements performed while on propranolol and again during the pindo lol study

There was a mean 13 2% decrease in $FEV_{1\,0}$/VC during propranolol therapy compared to a non treatment period ($p < 0\,01$) Following proprano lol withdrawal $FEV_{1\,0}$/VC increased by a mean of 14 1% ($p < 0\,01$) and did not differ significant ly from control

Compared to the pre propranolol and post propranolol FEV /VC there was essentially no change in $FEV_{1\,0}$/VC with either intravenous or long term pindolol therapy

Discussion

Beta adrenergic blockade has become an increasingly popular mode of treatment for supraventricular tachyarrhythmias In the first three parts of this series the newer beta blockers were shown to be as effective as propranolol at a similar degree of beta blockade[8,1] If these new compounds are to be uniquely useful they should be able with their other pharmacological proper ties to substitute for propranolol in situations where bronchospasm intermittent claudication or myocardial depression are potential problems

Propranolol blocks both cardiac (β_1) and smooth muscle (β) receptors and as confirmed by this study may aggravate bronchospasm in susceptible patients (β_2 receptor blockade) Some beta adrenoceptor blocking drugs have a degree of selectivity for β_1 receptors as opposed to β receptors and are said to lessen the frequency of bronchospasm in patients with asthma[11] The drugs with cardioselectivity included practolol and tolamolol (currently under scrutiny because of potentially serious adverse effects) metoprolol (recently approved by the FDA for use in hyper tension) acebutolol and atenolol These com pounds differ from propranolol by a substitution at the para position of the aromatic ring The cardioselectivity of these agents is not absolute and at higher doses (within the therapeutic dose range) β antagonism becomes apparent with the loss of the potential benefit of bronchoprotec tion[6]

Other beta receptor blocking drugs have a high degree of intrinsic sympathomimetic activity a property which has been claimed to lessen the risk of bronchospasm and congestive heart failure Although beta blockers by definition antagonize the actions of agonists some may paradoxically retain a degree of agonist activity with respect to the same receptor (intrinsic sympathomimetic activity) Initially this property was thought to limit the clinical usefulness of certain beta block ers (practolol acebutolol oxprenolol alprenolol and pindolol)[12] However clinical studies have not substantiated this claim and there is no evidence that beta blockers devoid of this effect (propranolol sotalol timolol metoprolol and atenolol) are more clinically efficacious

Pindolol (prindolol LB-46) one of the newer

beta adrenoceptor blocking drugs is milligram for milligram the most potent beta blocker currently available [13] and also has the most intrinsic sympathomimetic activity The drug possesses membrane stabilizing properties similar to those of propranolol During the initial clinical trials with pindolol the drug was thought to be cardioselective because it failed to precipitate bronchospasm in patients [14] However increased affinity for the β_1 receptor was shown not to be the cause of this selectivity and the intrinsic sympathomimetic effects of pindolol on bronchial smooth muscle (bronchodilatory) may have contributed to its beneficial effects in asthma [5] In fact practolol may also owe its well known bronchial sparing properties to its high degree of intrinsic sympathomimetic activity [1] If intrinsic sympathomimetic activity of beta adrenergic blockers does play a role in bronchoprotection this property would be more advantageous than cardioselectivity since intrinsic sympathomimetic activity is manifested at all dose levels whereas cardioselectivity is only manifested at the lower dose ranges [4, 5]

The results of this study demonstrate that pindolol (used both intravenously and orally) is a reasonable substitute for propranolol in therapy of patients with supraventricular arrhythmias and bronchospastic disease Subjectively 16 of the 18 patients with bronchospasm previously induced by propranolol noted *no* aggravation of their wheezing with either intravenous or oral pindolol therapy Objectively patients treated with pindolol showed no deterioration in FEV / VC on average compared to control whereas the same patients previously treated with propranolol had shown a marked deterioration in this lung function parameter Since pindolol does not exhibit cardioselectivity one must implicate its intrinsic sympathomimetic activity as the cause of the bronchoprotective effect seen in most of these patients

Other investigators have reported similar results In a large series by Beumer and Hardunk which compared pulmonary function in patients following treatment with propranolol pindolol practolol alprenolol and oxprenolol only practolol and pindolol were found to be bronchoprotective

Used as anti arrhythmic agents all beta blocking drugs manifest their action through beta blocking activity and not through quinidine like membrane depressant activity as was initially proposed [1] Nevertheless intrinsic sympathomimetic activity does not appear to interfere with clinical usefulness since multiple trials have shown pindolol to be as effective an antiarrhythmic agent as propranolol [1, 1] In this study 16 out of 18 patients with supraventricular tachyarrhythmias responded to intravenous pindolol compared to none of 18 with placebo and long term antiarrhythmic benefit was maintained in 12 of 16 patients with oral pindolol treatment These patients had had similar anti arrhythmic results with propranolol but could not tolerate the drug because of bronchospasm Thus judging from its antiarrhythmic effectiveness alone pindolol appears to be a reasonable alternative to propranolol

One might postulate that pindolol would be superior to propranolol where bronchospasm was itself aggravating the arrhythmia Another potential advantage of pindolol over propranolol might be seen in patients with sick sinus syndrome with a brady tachy presentation Once the tachyarrhythmia is eliminated propranolol may further depress the diseased sinus node resulting in a profound bradyarrhythmia Pindolol with its intrinsic sympathomimetic activity does not depress the sinus and AV node to the same degree as propranolol and may be better tolerated in patients with underlying conduction disease [18]

Extensive clinical trials using pindolol as an anti arrhythmic agent have been performed in Europe South Africa and Japan [1] The only previous American experience with pindolol in cardiac arrhythmias was reported by Aronow and Uyeyama These investigators treated 30 patients with supraventricular and ventricular arrhythmias who had no evidence of obstructive lung disease or congestive heart failure They found the intravenous drug to be extremely useful in atrial fibrillation (conversion to normal sinus rhythm and/or significant ventricular rate slowing) atrial flutter paroxysmal atrial tachycardia sinus tachycardia ventricular tachycardia and digitalis induced arrhythmias CHF was precipitated in only one patient

In studies comparing pindolol with other beta blockers the drug was shown to be as efficacious as propranolol practolol and alprenolol for treatment of supraventricular arrhythmias [15]

Conclusions

Ideally beta adrenoceptor blocking drugs should be avoided in patients with active bron

chospastic disease However pindolol (with its intrinsic sympathomimetic properties) may offer an effective alternative to propranolol in situa tions where a β blocker is indicated Whether or not the intrinsic sympathomimetic property of pindolol can protect patients with myocardial depression from further deterioration in their functional status has yet to be determined

Summary

Pindolol (LB 46) is a new beta adrenoceptor blocking agent with intrinsic sympathomimetic activity In order to evaluate the efficacy of pindolol in the treatment of patients with supra ventricular arrhythmias and propranolol induced bronchospasm 18 patients with paroxysmal supraventricular tachycardia atrial fibrillation atrial flutter multifocal atrial tachycardia or junctional tachycardia were treated with placebo followed by pindolol in intravenous and then oral form Following a no response placebo period (in all patients) intravenous pindolol converted six out of seven patients with paroxysmal supraven tricular tachycardia to normal sinus rhythm In six patients with atrial fibrillation three reverted to normal sinus rhythm and three remained in atrial fibrillation but with a slower ventricular response (less than 100 beats/minute) Of two patients with atrial flutter one converted to normal sinus rhythm while the other patient failed to respond Both patients with junctional tachycardia and one with multifocal atrial tachy cardia converted to normal sinus rhythm Long term oral pindolol therapy sustained these responses in most patients as documented by serial Holter ECG studies There was no deterio ration in indices of airway resistance (FEV /VC) in patients treated with pindolol (both intrave nously and orally) in contrast to a marked deterioration in FEV /VC in the same patients treated with propranolol Pindolol appears to be a reasonable substitute for propranolol in patients with bronchospastic illness who require beta blockade for control of supraventricular arrhyth mias

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Annotations

Refractory arrhythmia in the presence of congestive failure successful beta sympatholytic treatment

Beta adrenergic blocking agents such as propranolol inhibit the effects of all beta agonists on the mechanical behavior of heart muscle The negative chronotropic and inotropic effects of this beta blocker are well known In congestive heart failure cardiac performance is hi hly dependent upon adrenergic stimulation and autoregulatory phenomena can not adequately compensate when the heart is i olated from this stimulation For these reasons propranolol should be used with caution or not at all in patients with congestive heart failure Newer beta blockers have pharmacologic profiles which are quantitatively and qualitatively different from propranolol We report here the successful treatment of a patient in congestive heart failure with a life threatenin cardiac arrhythmia with one of these new beta blockers nadolol (Corgard)

A 60-year old man entered the hospital for congestive heart failure pulmonary edema multifocal premature ventricular contractions and tachycardia The patient s history included diabetes mellitus and hypertension and five previous hospital admissions for myocardial infarction congestive heart failure shortness of breath, orthopnea dyspnea on exertion and ascites

Physical examination revealed sli htly distended neck veins bibasal rales S normal S slightly accentuated S audible and S soft no murmurs were heard Abdominal examination revealed an obese nontender abdomen liver pan was 14 cm spleen tip and bowel sounds were normal Laboratory findings were not abnormal and the electrocardiogram (Fig 1) showed frequent multifocal PVCs with short episodes of frank ventricular tachycardia

In addition to his regular therapeutic regimen of digoxin (0 25 mg per day) furosemide (40 mg twice a day) potassium chloride pironolactone (25 mg four times daily) diazepam (5 mg four times daily) and NPH insulin (?0 u per day) Oral quinidine sulfate (300 mg every four hours) was added in an attempt to control the arrhythmia He was given a 2 gm sodium diet and was continuously monitored in our coronary care unit Within 24 hours, he experienced severe nausea and vomiting which was attributed to quinidine All oral medica tions were then stopped and intravenous procainamide and lidocaine were administered at a rate of 2 mg per minute in an attempt to control the cardiac arrhythmia Although this therapy produced partial remission in the frequency of ventricular extrasystolic beats the patient still experienced coupling with short bursts of ventricular tachycardia

Six months prior to this hospital admission the patient participated in a clinical pharmacology study of the antiar rhythmic effects of nadolol and experienced si nificant reduction in PVC frequency at that time Because of this previous successful therapy nadolol was administered (after informed consent was obtained) and all other antiarrhythmic medications were discontinued The initial dose was 10 mg every six hours Within 15 hours and a cumulative dose of 30 mg of nadolol the patient s PVCs were markedly reduced from 324 7 + 12.4 to 46 9 ± 11.5 × (Table I) Trigeminy and ventricular tachycardia which were present prior to nadolol therapy were absent after nadolol administration Ventricular ectopic beats were recorded by a two-channel

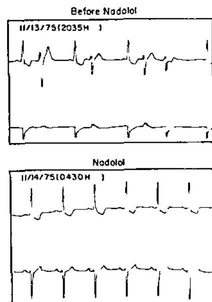


Fig 1 Electrocardiograms before and after nadolol.

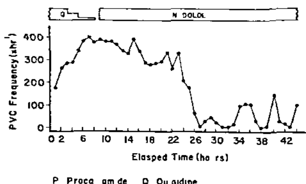


Fig 2 Hourly PVC frequency before and after nadolol.

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Table I Cardiac arrhythmias before and after nadolol therapy

	Cardiac arrhythmia		
	PVC/hr ± SE	*Bigeminy*	*V tach*
Before nadolol	324 7 ± 12 4	+	+
After nadolol	46 9 ± 11 5	0	0

Table II Usual high and low heart rate before and after nadolol therapy

	Heart rate		
	High	*Usual*	*Low*
Before nadolol	85	65	52
After nadolol	65	58	55

Table III Laboratory data

Parameter	*Admission data*	*Pre nadolol*	*Nadolol period Day 1*	*Nadolol period Day 7*
WBC	6 400	8 600	10 700	—
Hemoglobin	11 1	11 3	11 7	—
Hematocrit	3? 9	34 2	35 7	—
RBC	3 74	3 8?	4 02	—
Serum Na	140	136	133	137
Serum K	4 9	5 0	5 4	4 6
Serum Cl	106	92	92	99
Serum Co	26	33	31	29
BUN	19	39	51	34
Creatinine	—	1 8	? 6	1 8
CPK	19	14	—	—
LDH	6?	5	—	—
SGOT	14	9	—	—

Holter 24 hour monitor and were analyzed by an Avionics Electrocardio-Scanner with an integral arrhythmia computer A plot of the PVC frequency appears as Fig 2 Table II shows the reduction of cardiac rate from approximately 65 beats per minute to approximately 58 beats reflecting the presence of beta blockade The clinical laboratory data obtained upon admission prior to nadolol after one day of nadolol and 7 days after nadolol therapy are presented in Table III and do not suggest any nadolol toxicity

During nadolol therapy the patient did not experience any direct myocardial depression generally present in a patient with congestive heart failure who has received a beta adrenergic blocking agent This may be related to the lack of effect of nadolol on myocardial cellular membranes however this remains to be confirmed

After ten days the patient was discharged from the hospital with a therapeutic regimen including his usual medicati[on] but excluding any antiarrhythmic agents other than nad[olol] (80 mg once daily)

The response of this patient to nadolol suggests that nado[lol] may be particularly useful in the treatment of card[iac] arrhythmias in patients who have borderline or overt cong[es]tive heart failure Substantiation of this usage awa[its] controlled clinical trial

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On the bioavailability of digitalis after single oral doses

In the last decades several investigators focused their studies on digitalis and many works were performed on the pharmacokinetics of cardiac glycosides (CG)

One of the most troublesome aspects of digitalis pharmacokinetics is their bioavailability In fact it was demonstrated that there is a significant interindividual variation in the CG bioavailability as the area under serum concentration/time curve (AUC) therefore many authors believe the urinary excretion to be the most reliable index of bioavailability since the very high levels reached in the urinary drug concentration lower the interindividual differences. On the other hand all the investigators agree that in the same person the bioavailability (expressed as AUC) is always constant

Six healthy young men received single oral doses (1 mg in elixir) of beta methyl-digoxin (BMD) for 6 weeks on the same day of the week but at different hours each time A randomization schedule was applied Meals were served at 8 00 A M 1 00 P M and 8 00 P M and no food was permitted inbetween Rest lasted from 11 30 P M to 7 30 A M Digitalis serum levels were measured in duplicate by RIA (Becton & Dickinson) in blood samples taken at 0 0 5 1 2 4 8 1? 20 and 36 hours from ingestion time AUCs were computed by the trapezium rule Usual statistical analyses and the Cosinor test were performed.

We obtained 36 individual digitalis AUCs The limits of variability of the total areas were 109 87 to 34 6 ng /ml /hr Using the Cosinor test a significant circadian rhythm of the AUC is seen with Mesor (i.e the mean level of the function) = 55 58 ng /mL/hr with Acrophase (i e the peak timing of the variable) = 10 05 A M and with Amplitude (i e the maximum of the function from M) = 6 71 ng /ml /hr The total area under the serum digitalis curve is an index of the glycoside bioavailability It has been seen as previously mentioned that each individual subject tends to absorb a constant amount of digoxin Our results show that a sin le dose of BMD given at different hours of the day can be absorbed differently even in the same subject

The examination of the 36 individual serum curves reveals that the curves obtained with a nocturnal BMD administration have an exponential phase whereas those obtained with diurnal BMD administration do not present this exponential phase but have instead a late second peak In all of the six subjects receiving BMD during the daylight hours the digitalis serum concentration 12 or 20 hours after ingestion time is significantly higher than the concentration just before the second peak with exception of the 8 00 A M administration Using the Cosinor test a significant circadian rhythm of the second peak area is seen with Mesor = 43 78 ng /mL/hr with Acrophase = 10 07 A.M and with Amplitude = 6 78 ng /mL/hr On the basis of the Cosinor test it is evident that the second peak area values and the total area are similar in phase Also the total area values and the second peak area values are significantly correlated ($r = 0\,95$ $p < 0\,001$) According to the Aldous and Thomas hypothesis and to the data of BMD

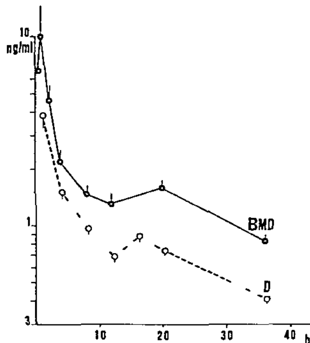


Fig 1 Digitalis serum curves obtained in six subjects after administration of BMD (1 mg orally) at 12 00 A M and the curve obtained in five subjects after the administration of di oxin (1 mg orally) at 11 00 A M

metabolism (about 50 per cent demethylated to digoxin) we would suspect a priori, that the second peak observed with diurnal BMD administration was related to conversion to digoxin by the GI tract and/or by the liver This hypothesis was not confirmed by our results obtained via administration of digoxin In fact, the digitalis serum curve obtained with the 11 00 A M digoxin administration in five healthy men in the same conditions as the previous six (Fig 1) evidenced a second late peak very similar to BMD Probably the authors who previously investigated digoxin kinetics did not often observe a late second peak because they administered the drug early in the morning In fact we have observed that the increment of BMD serum level 8 to 1? hours after an ingestion time at 8 00 A.M is not statistically significant because the second peak is not very evident Another reason that this second peak has not been discussed much in the literature is that a few investigators whose results did demonstrate it failed to note it in their reports A few other authors have noted its existence for th majority of the cardioglycosides (CG) for example digoxin BMD digitoxin proscillaridin lanatoside C etc Kuhlmann and colleagues, on the basis of chromatography suggested a metabolization by the GI flora and/or liver into metabolites other than digoxin but this hypothesis is not

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perfectly satisfying because we demonstrated that the second peak always occurs around 4 00 to 8 00 A M in the morning independent of the administration hours

The presence of a second peak is another reason besides those already given by Wagner for doubting that the CG kinetics are of the first order In addition it is important to know if the existence of this second peak has a clinical significance It is toward this end that we are studying on the basis of the administration time the eventual modifications of the bioavailability of digitalis during chronic therapy

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Alcohol and myocardial infarction in hypertensive men

Moderate or heavy alcohol consumption may protect against coronary artery disease and is also associated with raised blood pressure Mathews has suggested that hypertensive subjects who use alcohol heavily may have relative protection from ischemic heart disease Since the inception of the Glasgow Blood Pressure Clinic in 1969 alcohol intake and a history of ischemic heart disease have been recorded routinely and in a standard manner for each new patient Alcohol intake is graded simply as nil occasional frequent or heavy The validity of this method of assessment was established by demonstrating a highly significant relationship with biochemical evidence of liver dysfunction

Data for 1 305 hypertensive men aged 30 years or over who entered the clinic before June 1977 were examined A history of myocardial infarction was given by 65 (5 0 per cent) patients. Myocardial infarction was recorded in 6 7 per cent of non-drinkers in 6 0 per cent of occasional drinkers in 3 4 per cent of frequent drinkers and in 0 9 per cent of heavy drinkers and these differences were significant (χ = 8 5 P < 0 05) Probable or definite angina was recorded in 135 (10 3 per cent) patients with 11 4 per cent in non-drinkers 11.5 per cent in occasional drinkers 9 2 per cent in frequent drinkers and 5 2 per cent in heavy drinkers The trend towards less angina with increasing alcohol intake was not significant (χ = 4 9 P > 0 1) Recorded alcohol intake fell slightly with increasing age and the data for myocardial infarction were therefore examined separately in 10 year age groups (Table I) Increasing alcohol consumption was associated with a decreasing frequency of myocardial infarction at all ages although this was significant only in the largest group those aged 50 to 59 years The approximate relative risk of myocardial infarction in men aged 50 to 59 who took alcohol occasionally or not at all was 3 4 (95 per cent confidence limits 1.2 to 9.9) when compared with those using alcohol frequently or heavily The possibility that alcohol and myocardial infarction might be related through other risk factors was examined in patients aged 50 to 59 years (Table II) There was no association of alcohol intake with age weight height initial blood pressure or plasma total cholesterol Men who drank frequently or heavily were cigarette smokers more often (χ = 8 0 P < 0 0) and also smoked more heavily (χ = 11.3 P < 0 0)

It must be emphasized that these data are for a history of myocardial infarction not for new events occurring dur g observation and several interpretations are therefore possible It could be that myocardial infarction in heavier drinkers carries a higher mortality rate so that they do not survive to reach hospital clinics although there is strong evidence that this is not the case An apparent excess of myocardial infarction in infrequent drinkers would result if episodes in heavy drinkers were clinically silent undiagnosed or d ned

Table I Frequency of a history of myocardial infarction in male hypertensive patients tabulated by age and alcohol consumption

Alcohol consumption	*Age (years)*			
	30-39	*40-49*	*50-59*	*60+*
Nil	1/19 (5.3%)	3/56 (5.4%)	6/65 (9.2%)	3/53 (5.7%)
Occasional	0/96 (0.0%)	9/189 (4.8%)	22/256 (8.6%)	9/130 (6.9%)
Frequent	0/52 (0.0%)	6/117 (5.1%)	4/116 (3.4%)	1/41 (2.4%)
Heavy	0/22 (0.0%)	1/49 (2.0%)	0/31 (0.0%)	0/13 (0%)

Nil and occasional alcohol versus frequent and heavy alcohol $\chi^2 = 4.80$ df = 1 $P < 0.05$

Table II Risk factors for ischemic heart disease in 468 hypertensive men aged 50 to 59 years related to alcohol consumption Mean ± standard deviation

	Alcohol consumption	
	Nil or occasional	*Frequent or heavy*
Number of patients	321	147
Age (years)	54.4	54.5
Weight (Kg)	75.1 ± 11.4	76 ± 11.2
Height (cm)	169.8 ± 7.9	168.6 ± 7.3
Blood pressure (mm Hg)		
Systolic	185 ± 28	184 ± 27
Diastolic	113 ± 17	112 ± 16
Plasma total cholesterol (μmol/L)	6.2 ± 1.1	6.3 ± 1.2
Cigarette smoking		
Never	132 (41%)	42 (29%)
Previous	40 (12%)	20 (14%)
Current	137 (43%)	82 (56%)
Cigarettes per day		
1-10	36 (11%)	10 (7%)
11-20	76 (24%)	43 (29%)
21-30	18 (6%)	19 (13%)
31	6 (2%)	9 (6%)

$\chi^2 = 8.03$ df = 2 $P < 0.02$
$\chi^2 = 11.26$, df = 3 $P < 0.02$

by the patient or if patients suffering a myocardial infarction reduced, or understated their alcohol intake. These possibilities cannot be excluded from the available data.

While conceding that these interpretations are tenable the results are consistent with other studies suggesting that alcohol may protect against coronary artery disease and more specifically against myocardial infarction. The low frequency of myocardial infarction in men aged 50 to 59 using alcohol frequently or heavily could not be attributed to differences in age weight blood pressure or cholesterol, and indeed an excess of myocardial infarction might have been expected since they smoked cigarettes more often and heavily. Despite the larger number of patients with angina there was no significant relationship with alcohol intake suggesting that any protective effect of alcohol may be less for angina than for myocardial infarction. Acute alcohol ingestion reduces the exercise time required to produce pain in anginal patients, and for a given degree of coronary atherosclerosis alcohol users may be more often symptomatic. Alternatively chest pain caused by alcoholic cardiomyopathy may be diagnosed as angina and thus may obscure a relationship between alcohol and chest pain due to coronary disease.

The evidence that alcohol may protect against myocardial infarction is far from conclusive and even if cause and effect can be established, I doubt whether these observations would have direct therapeutic implications. The amount of alcohol required to "protect" against myocardial infarction was associated with a significant excess of liver dysfunction and would probably prove injurious to health in other respects, and socially unacceptable. However the mechanism through which alcohol exerts any protective effect would be of great interest bearing in mind evidence that drug treatment of hypertension has so far failed to reduce the incidence of myocardial infarction. Barboriak has suggested that elevation of high-density lipoproteins by alcohol may modify the atherogenic effects of low-density lipoproteins.

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Of 'The quality of life'

It is regularly emphasized that coronary bypass surgery is justified, in spite of expense hazards, and even failure to prolong life because the operation almost invariably improves the quality of life by reducing the incidence of episodes of angina pectoris in 85 per cent or so of patients This is arbitrarily attributed to "revascularization" of the heart However it was shown in 1959 and 1960 that merely incising and suturing the skin over the precordium also reduces the incidence of angina pectoris in many patients, thereby "improving the quality of life" This latter operation carries no risk and is inexpensive Furthermore general physicians and even cardiologists can perform this operation without having to impose upon the valuable time of their cardiovascular surgical colleagues. Therefore how can one justify expensive hazardous coronary bypass surgery on the basis of improvement of the quality of life when a mere precordial cutaneous incision will improve life as effectively?

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Letters to the Editor

Meaning of elevated CK MB

To the Editor

Drs. Roberts and Sobel (AMERICAN HEART JOURNAL 95 5?1 1978) rendered great service to the profession in laying many of the ghosts confounding the interpretation of the clinical significance of creatine kinase isoenzymes but Dr Roberts has raised new ghosts in his reply to the comments of Marmor and associates in the February 19,9 issue of the JOURNAL (97 ?69 1979)

The issue is much wider than the reliability of CK MB as a predictor of acute MI and certainly not as simple as ischemia versus necrosis We would re state and answer the questions as

1 Does a serum elevation of CK MB point to a problem involving the heart? The answer is a plain *Yes*

2 Is this problem necessarily necrosis (or ischemia) The answer is an equally plain *No*

Roberts and Sobel made it admirably cl ar that a serum elevation of CK MB tags the heart as the source There are rare exceptions but provided the CK MB is measured as such (and not as non M CK) the exceptions can be pecifically excluded from consideration Thus there is no argument on our affirmative answer to Question 1

Dr Roberts is in rror in denying the cardiac origin of the CK MB elevation in the cases reported by Marmor and colleagues We often see and others have reported patients with increased CK MB activity and normal total CK Our laboratory no longer holds to the policy of cancelling a request for CK iso determination on the grounds that the total CK is within normal limits. Upper limits of normal CK tot vary widely among authors (our range is 30 to 90 U /L) but the range of normal CK tot (up to 65 U /L in Roberts laboratory) permits a twofold or threefold rise in the CK level of a patient with an average or low ba eline CK activity without exceeding the upper limit Accepting the cardiac MM MB ratio of 85 15 cited by Roberts we can readily postulate a patient with a baseline CK tot of 30 U /L sustaining a cardiac event resulting in the addition to the serum level of 7 U /L CK MM and 4 U /L CK MB without reaching the upper limits of normal The hi her levels of CK tot observed in acute MI may be misleading in experi mental infarction the major source of the observed CK MM rise is from extracardiac sources

The cardiac events which may lead to cardiac enzyme release are not limited to variants of acute MI and are not all sub umable under the heading of ischemia without gross laxity in use of the term minor blunt precordial trauma, cardioversion arrhythmia cranio cerebral disease or injury (mediated by catecholamine release) cardiac surgery cardio myopathy cation imbalance and drug intoxication

To challen e our ne ative answer to Question ? is to ignore a large and growing body of evidence to the contrary Roberts comparison of the molecular wei hts of myo lobin and CK is a red herring Perhaps (we would say probably) myoglobin is indeed released from the myo ardial cell only after necrosis or severe injury but the same does not hold for cardiac enzymes

A low baseline level of cardiac enzyme leakage is the concomitant of normal myocardial cell metabolism This low level is maintained by a process of "active retention" The process is energy-dependent and leakage at higher levels is a mea ure of the degree of deficiency in the metabolic maintenance of the functional integrity of the myocardial cell membrane The metabolic effects resulting in increased leakage may be and often are wholly or partially reversible The viability of the myocardial cell is not necessarily jeopardized

In the clinical setting an elevation of CK MB activity ignifies an adverse effect on the myocardial cell but that effect is not necessarily either necrosis or ischemia

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Reply

To the Editor:

I entirely agree that plasma MB CK may be increased without total plasma CK activity being increased outside the normal range. In the previous letter (Am. Heart J 97:269, 1979) I stated that if the plasma MB CK increases so must total CK as illustrated by the example given by Dr. Lindsey and associates so we are in complete agreement. However, if MB CK is released from the heart or skeletal muscle myoglobin should also be released. Dr. Lindsey and colleagues referred to the preceding statement as a "red herring" but give no reason. I would like to state that my conclusion is based on certain scientific data. (1) Following exercise myoglobin, CK, and LDH are released with myoglobin appearing in the plasma prior to CK and LDH. (2) Following myocardial infarction in dogs and in man myoglobin release precedes CK and LDH. (3) In the article quoted by Lindsey and associates (Reference 13) it is stated and I quote "considering the intra-extracellular concentration gradients and molecular weights of these enzymes (Table I) the highest release rate corresponds to the highest concentration gradient and the lowest molecular weight and vice versa."

I shall be very surprised if future investigation show that myoglobin with a molecular weight of 17,000 is released only with necrosis and that of CK with a molecular weight of 82,000 released with ischemia without necrosis, but this hypothesis despite its illogical content would stimulate further research in the field.

I agree with Dr. Lindsey and colleagues that release of MB CK from the heart may occur subsequent to any form of cardiac injury and not just that of ischemic nature. Dr. Lindsey and coworkers stated that MB CK may be released subsequent to ischemia without necrosis. As stated in our review (95:521, 1978) and also in the Letters to the Editor (97:269, 1979) it is possible that release of MB CK from the myocardium does not always reflect cell necrosis; however, there is no scientific data supporting this conclusion at the present time. It is perhaps more important to the scientific community to realize it is only an hypothesis and requires further scientific exploration. The evidence cited by Lindsey and colleagues regarding ischemia refers to isolated perfused heart preparations which were made anoxic for 20 minutes. First of all, the perfused heart, the moment it is removed from the organism, is a dying preparation. Secondly 20 minutes of anoxia is probably equivalent to 1 to 2 hours of ischemia in the intact organism, a situation known to lead to irreversible necrosis. In none of these experiments is there morphologic data. Release of MB CK from the heart subsequent to transient reversible injury remains to be proven.

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IV quinidine administration

To the Editor:

I wish to correct a statement made by Drs. Woo and Greenblatt in the Annotations section of the December 1978 issue of American Heart Journal. They claim that I administered quinidine intravenously at a rate of 0.5 to 1.0 mg/kg/min. to nine hospitalized patients. In fact, the rate of administration was 6.1 mg per minute which would be 0.09 mg/kg/min. in an average size male.

I would suspect that an infusion of 0.5 to 1.0 mg/kg/min. (35 or 70 mg/min. in an average male) would be associated with a much higher incidence of adverse effects than is seen with slower administration.

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Reply

To the Editor:

In response to Dr. Conrad's letter, we concur with the error in our manuscript and agree with Dr. Conrad's observation.

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Boston, Mass. 02114

Book reviews

A Self teaching Atlas of Echocardiography By C Z. Naggar Bowie Maryland 1978 The Charles Press Publishers 275 pa es

Numerous books on echocardiography (ECHO) are appearing The advantages of one over another are matters of opinion This book is introduced as a self teaching atlas The correlation of the ECHO with the clinical data is an important objective of this book but the reader would expect all of the clinical data to be presented to enable a thorough correlation These additional data should include the roentgenograms, electrocardiograms and other minimal laboratory data Regardless a brief summary of the clinical data from the history and physical examination are at least presented It is rather interesting that body surface area (BSA) rather than height and weight of the patients is indicated Body weight and height can be readily measured with an error of less than 1 per cent whereas body surface area obtained from a normogram or by calculations from height and weight introduces an enormously large error Those who express body size by BSA in their clinical and experimental studies should study the original investigations upon which BSA is obtained Furthermore most of the readers of this book most probably employ the more accurate expression of body size by height and weight anyway Furthermore an obese short man and a tall, muscular one may have the same BSA but are quite different in clinical consideration Readers will find this apsect of the clinical data less meaningful This reviewer finds some of the ECHO diagnoses difficult to understand For example on page 23 the author states that the mitral valve prolapse is hemodynamically insignificant This may be so but how can an interpreter of an ECHO know at any given moment what the hemodynamic significance is? In addition on that same page 23 the diastolic IVS thickness was found to be only 6 mm This is rare if ever true grossly anatomically in an 18 year old person Could that have been an error of the method or of measurement Nevertheless if critically and thoughtfully read and studied in association with other books and original publications in the literature this book is a useful one It should help beginners to not only l arn ECHO but also to become acquainted with the practice of ECHO in another area of the world In general and in spite of specific details concerned with differences of opinion this is a good atlas

The Pacemaker and Valve Identification Guide By Dryden Morse and Robert M Steiner Garden City New York 1978 Medical Examination Publishing Co 116 pages

This manual shall serve a useful purpose to cardiologists cardiac surgeons and radiologists. The manual includes a physical description of the current pacemakers used in the practice of medicine The physical and electrical characteristics of each is described as well as the roentgenographi configuration of the battery pack. This latter aspect of the book can be extremely valuable when the original description of the unit supplied by the manufacturer is not available during a crisis Another useful feature is the discussion of the effect of electric and magnetic fields on the pacemaker This is a very useful manual

Peripheral Circulation Edited by Paul C Johnson Somerset New Jersey 1978 John Wiley & Sons Inc 369 pages Price $29.95

This book on the peripheral circulation edited by P C Johnson is intended for vascular physiologists but should interest and benefit clinicians and surgeons who are involved in the management of peripheral vascular diseases Although peripheral diseases and pathophysiologic states are not discussed a knowledge of the normal physiology of the peripheral blood vessels is necessary for successful and intelligent care of vascular disease states The book is divided into 13 parts with chapters on general fundamental principles of peripheral vascular physiology and chapters on the circulation to the kidney skin muscles myocardium alimentary canal liver adipose tissue and brain The book is not only well written but also contains many interesting and important facts As is current practice the references cited were published recently Excellent older references were ignored This is a good book but it is not encyclopedic It emphasizes current research and fundamental concepts of the circulation This is a fine addition to the medical literature

Books received

The Isolated Heart-Lung Preparation By P H Huisman and J J Schipperheyn The Hague The Netherlands, 1978 Martinus Nijhoff Medical Division 41 pages

Habitual Physical Activity and Health By K. Lange Andersen R Masironi J Rutenfranz and V Seliger Copenhagen 1978 World Health Organization 188 pages Price $12.50

Noninvasive Cardiovascular Diagnosis Edited by Edward B Diethrich, Baltimore 1978 University Park Press 524 pages Price $39 50

Physical Activity and Aging By Roy J Shephard M D Ph.D Chicago 1978 Year Book Medical Publishers Inc 353 pages Price $17 95

Clinical Nephrology second edition By Solomon Papper M D Boston 1978 Little Brown & Company 633 pages Price $22 50

Biology of Brain Tumors Edited by O D Laerum D D Bigner and M F Rajewsky Geneva Switzerland 1978 International Union Against Cancer 209 pages. Price 1_ Swiss francs.

Society of Nuclear Medicine Meeting

The Fourth Western Regional Meeting of the Society of Nuclear Medicine will be held at the Monterey Conference Center in Monterey, California, on October 18 through 21, 1979. The program will consist of invited lectures and contributed papers. Commercial companies are invited to exhibit. For further information, contact: Jon Lasker, P.O. Box 4070, San Francisco, Calif. 94140. Telephone (415) 64-1068.

Symposium on Unstable Angina

A symposium on unstable angina pectoris: its pathophysiology, diagnosis, and management will be held in Toronto, Ontario, Canada, on November 9 and 10, 1979.

For further information, contact: Bernard S. Goldman, M.D., Room 128, University Wing, Toronto General Hospital, Toronto, Ontario, Canada M5G 1L7.

International Symposium on Coronary Arteriography

The Cleveland Clinic Foundation is sponsoring an International Symposium entitled "A Generation of Coronary Arteriography" on October 18 through 20, 1979, at Stouffer's Inn On The Square in Cleveland, Ohio.

For further information regarding this symposium, please contact: Center for Continuing Medical Education, The Cleveland Clinic Educational Foundation, 9500 Euclid Ave., Cleveland, Ohio 44106. Telephone (216) 444-5614.

Einthoven Symposium

The Einthoven Symposium, dedicated to an examination of cardiology's past and present, will be held in Leiden, The Netherlands, on November 1 and 2, 1979. Included will be discussions on the history of heart catheterization and Angiocardiography, present trends in cardiology, development of cardiac surgery, and historical and modern cardiovascular control concepts. The symposium will be limited to 150 participants. Inquiries should be addressed to: Dr. H. A. Snellen, Cardiology Department, University Hospital, Leiden, The Netherlands.

Computers in Cardiology

The sixth international conference on topics related to the application of computers to cardiovascular research, diagnosis, and treatment will be held in Geneva, Switzerland, from September 26 through 28, 1979. The meeting is co-sponsored by the American Heart Association, the European Society of Cardiology, the National Institutes of Health, and the IEEE Computer Society. In the past, the meetings have been attended by 200 to 300 scientists from both medical and technical disciplines. Proceedings of the conference will be *published by the IEEE. For information regarding this meeting* write: Computers in Cardiology, Centre de Cardiologie, Hôpital Cantonal, 1211 Geneva 4, Switzerland.

Society for Clinical Trials

The Society for Clinical Trials has recently been organized to promote the development and exchange of information on clinical trials methodology and on research using similar methods. The Society plans to achieve these goals through meetings and publications and by attracting members from various disciplines. Membership is open to anyone interested. For further information and to apply for membership, please write to Dr. C. R. Klimt, Secretary, Society for Clinical Trials, Inc., 600 Wyndhurst Ave., Baltimore, MD 21210.

Pediatric Echocardiography Course

The Fifth Annual Pediatric Echocardiography Course will be held on October 15 through 19, 1979, in Tel Aviv, Israel. The course is sponsored by the American Society of Echocardiography and by H.E.L.P. Direct inquiries to: Pediatric Echocardiography Course, 4313 Placita Lanuco, Tucson, Ariz. 85718, or telephone the Course Director, Dr. Stanley J. Goldberg (602) 626-6508.

American Heart Journal

October 1979 Volume 98 Number 4

Editorial

Fats and arterial disease

Sir John McMichael
London, England

The whole adult population is exposed to a greater or lesser degree to the ultimate hazard of arterial obstruction complicating atherosclerotic lesions. Because lipid deposition occurs in 50 per cent of these lesions [1] it has been assumed that deposition of cholesterol from the blood is a contributory factor in this development. There is indeed a statistical association of higher cholesterol levels with the later development of obstructive arterial lesions, but this finding has only a limited predictive value and statistical association has been misinterpreted as causative when it may be merely an association due to other factors. An immense effort has been devoted to the reduction of cholesterol levels in the blood by diet and by drugs [2-4] and it must now be concluded that these efforts have had no detectable influence on the course or development of coronary heart disease.

Nevertheless there is a continuing flow of propaganda from epidemiologists, governments [5] and commercial organizations promoting a dietetic change from natural saturated animal fats to polyunsaturated fats. These represent a quite unwarranted extension of hope over experience. The lesions produced by butter feeding are quite different in histological and gross appearances from the spontaneously occurring atheromatous lesions in man. Experimentally produced atheroma involves elevations of blood cholesterol which are far higher than those seen in the human disease and excess fat is deposited outside the vessels in liver, spleen, and elsewhere producing a total picture of lipidosis totally dissimilar from the human condition. Furthermore, these fat fed lesions resemble more closely the fatty streaks often seen in the arteries of children which have a different distribution and a different histology from the fibrous atheromatous plaque to which they seldom develop. In human atheroma the earliest lesion contains no visible fat which only appears at a later stage of the lesion and not in all lesions ("pearly" plaques). Thus critical microscopic study in man gives no support to the idea that cholesterol is an essential preliminary for the development of the plaque but it is rather a later complication. Detailed studies at autopsy and also in life have also failed to show any correlation between the severity of the developing arterial obstruction and the level of the blood cholesterol. Elevations of blood cholesterol in man resulting from thyroid ablation, nephrosis, etc. are not accompanied by any enhanced development of coronary artery disease.[3] Varieties of frugal dietetic habits of religious orders[1] and ethnic groups have shown no relation of coronary heart disease to animal fat intake and indeed in India it was shown that there was a higher incidence where the fat intake was low.[1]

Action of diets and drugs

The reduction of fat intake in survivors of coronary episodes did not have any effect on recurrences or mortality, and similar negative

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effects were noted in a trial extending over 6 years from the substitution of soy bean oil (polyunsaturated) for butter in nearly 400 survivors of myocardial infarction. A secondary prevention trial in Sydney has indeed shown that the control patients on a free diet had a significantly better survival rate than those on a polyunsaturated fat diet. The much quoted trials in Finnish mental hospitals and in Los Angeles Veterans hospital are the only ones which favored the polyunsaturated fat diets. Both trials however have been severely criticized for poor statistical organization and indeed the Los Angeles trial was not regarded by its authors as supporting any prospect of benefit from dietetic change.

The blood cholesterol lowering effects of polyunsaturated fat diets and the drug clofibrate are mediated by switching cholesterol into the liver where it is excreted in the bile and contributes to the formation of gallstones. These complications are heavily and convincingly underlined in the recent primary prevention trial of clofibrate involving over 11 000 subjects. The effect of clofibrate in preventing coronary artery disease was unconvincing and the over all death rate was higher with a suspicious increase in upper intestinal carcinoma. This complication of changes in biliary acid excretion has also been noted by others. Since these are unacceptable hazards the authors of the primary prevention report do not recommend clofibrate in prevention. The same recommendation should now be extended to polyunsaturated fat diets which are suspect for the same reason.

Polyunsaturated fat diets seem to incorporate certain hazards. Certain vegetable oils have shown to be more damaging to the vascular endothelium than others. For example Wissler's group has shown that there is a good deal of scarring in the intima in the lesions which are produced by peanut oil and cocoanut oil. This scarring is virtually absent in experimental animals fed with butter which produces much less scarring in "foam" cell lesions which Wissler calls "similar to the earlier lesions i.e. fatty streaks which most pathologists now consider to be harmless.[3] Following the recognition that rape seed oil is unsuitable for cardiac metabolism and toxic to the hearts of Sprague Dawley rats other vegetable and now fish oils have fallen under suspicion.[2] Long chain (C22) fatty acids have been shown to damage the hearts of cynomolgus monkeys[4] which are sufficiently near primate relatives to call for the exercise of caution in the use of these diets in man.

A third point is that in the hardening of vegetable oils to make margarine the cis double bonds of the unsaturated fats can be transformed into trans fatty acids, the cholesterol esters of which have been shown to be much more sclerogenic than those of the naturally occurring cis forms.[5]

Before we make major recommendations to increase polyunsaturated fat consumption in human dietetic patients these observations alone should command caution.

The Israeli experience

Analysis of the subcutaneous fat reflects by and large the composition of the food ingested much more accurately than dietetic inquiries of the composition of various meals. The study at the Hebrew University by Professor Blondheim and his colleagues[6] has demonstrated that both in subcutaneous fat analysis and also on analysis of the food consumed in Israel from food tables the composition of the Israeli diet averages about 1 to 1 polyunsaturated–saturated fat. This is the highest proportion of polyunsaturated fats of any country in the Western world and indeed this corresponds with the McGovern Committee's recommendation for the prevention of coronary disease in the United States. It is notable however that Israel is one of the countries which comes high in the league table for the incidence of coronary heart disease which is three-quarters that in the United States per unit of population. The Bedouin Arabs who are alleged to have little coronary heart disease while living in the natural nomadic existence in the desert begin to develop coronary artery disease when they come into the Israeli towns to work. There they acquire a higher polyunsaturated fat ratio in their subcutaneous tissues. It is thus apparent that polyunsaturated fats in the diet do not prevent coronary heart disease in this large population studied under natural conditions.

Discussion

The writer does not subscribe to the view that atheroma is a nutritional disorder caused by dietetic imbalances but rather it is a localized

disorder due to the effects of trauma infection strain injury at various susceptible points in the complicated anatomy of the circulation Branching points are especially vulnerable and every pathologist is aware of the jet lesions which develop where a narrowing creates a hose nozzle stream impacting on a particular area on the distal vessel wall Stehbens[2] has shown experimentally that in arteriovenous fistulae in the sheep (which has a very low level of blood cholesterol) atheromatous lesions can develop due to the turbulence in the circulation at these points and also on the venous side of the vibrating arteriovenous communication where pressures are lower[2]

The sequence of events in the development of atheromatous lesions have been carefully studied by Dr Elspeth Smith and by others and this is not the place to summarize these researches A breach in the intima occurs with leakage of plasma materials under the intima accompanied by proliferation of the underlying smooth muscle cells deposition of fibrin and later of cholesterol The severity of the lesions has nothing to do with the level of cholesterol in the blood The injury can be mechanical or infective as has recently been shown for virus induced atheroma[2] This opens our minds to other possibilities

However at the time when these damaging effects are taking place in the vessel wall there is always the possibility that the lesion could be exaggerated by the presence in the circulation of certain products which could make the condition rather worse For this reason natural animal fats are much less likely to contribute to damage to the vessel wall than some of the processed hydrogenated oils in margarines

Conclusion

There is no need for the public to change the nature of its fat consumption towards margarines Various factors associated with vegetable oils can certainly be more damaging than the natural animal and dairy fats which *in excess* have been shown to produce much more innocent depositions in the blood vessel walls The time has come to avoid making any substantial change towards polyunsaturated fats in the diet as this change will not prevent coronary disease but could possibly have other damaging effects on the heart and circulation

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Information for authors

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Clinical communications

Temporary atrial standstill

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Carl V Leier MD**
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Temporary abolition of atrial activity with toxic doses of digitalis or digitalis and quinidine as well as anoxia was first demonstrated in experimental animal models at the turn of the century Sporadic reports of atrial standstill in man followed these episodes most often occurred in the setting of drug treatment (i e digitalis quinidine) of atrial fibrillation These early reports lacked intra atrial electrogram recordings to confirm the absence of atrial electrical activity and relied upon the surface electrogram and occasionally fluoroscopy More recently well documented cases of persistent and transient atrial standstill have been reported A variety of structural lesions have been associated with persistent atrial standstill and include muscular dystrophy familial amyloidosis Chagas disease and atrial degenerative disease of unknown etiology atrial inexcitability has been a feature of this group A range from normal to markedly suppressed atrial excitability exists in the patients with transient atrial standstill secondary to such diverse conditions as hyperkalemia systemic lupus erythematosus diphtheria infarction and post open heart surgery We report the occurrence of temporary atrial standstill with intact atrial excitability in three patients undergoing electrophysiologic investigation This association suggests the concurrence of sinoatrial disease impaired ventriculo atrial conduction and suppression of ectopic atrial foci

From the Division of Cardiology Ohio State University College of Medicine Columbus, Ohio
Supported by a research grant of the Central Ohio Heart Chapter American Heart Association.
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Method

All patients were studied after full explanation was given and informed consent was obtained No premedication was administered Two bipolar No 5 pacing catheters were positioned in the high right atrium for atrial pacing and recording respectively A bipolar esophageal catheter was utilized to record the left atrial electrogram A six pole catheter was positioned across the tricuspid valve for low right atrial and His bundle recordings (except patient P R who had a tricuspid prosthesis) Recordings during spontaneous rhythm atrial pacing and atrial premature depolarizations were made using an Electronics for Medicine recorder at a paper speed of 25 to 100 mm/sec The atrium was paced at 1½ times threshold with a 2 msec duration pulse via a Grass Instrument S 88 pulse stimulator and isolation unit Pharmacologic intervention was utilized as necessary to fully evaluate the conduction system

Patient reports

Case No 1 R M a 37 year old Caucasian male had noted an irregular pulse three years prior to admission One year prior to admission he was found to be in atrial flutter when he presented with complaints of fatigue and myalgias He was medically converted to sinus rhythm with digoxin and quinidine but similar symptoms

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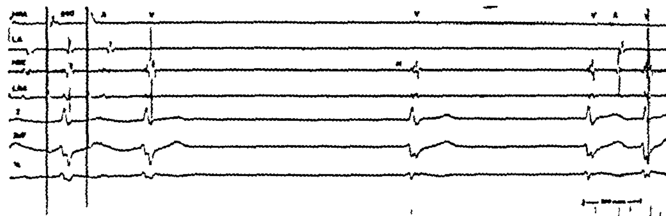


Fig 1 After atrial pacing (AA – 200 msec) is terminated temporary atrial standstill (3.8 seconds) occurs. Note the junctional beat preceded by a His bundle deflection does not conduct retrogradely to the atria *HRA* high right atrium *LA* left atrium (esophageal) *HBE* His bundle electrogram *LRA* low right atrium

recurred seven months later and atrial flutter was converted with DC countershock Holter monitor recordings revealed occasional episodes of probable sinoatrial block Because of these findings and a history of lightheaded spells he was referred for electrophysiologic evaluation Physical examination was entirely normal as were baseline serum and blood laboratory values The electrocardiogram revealed sinus rhythm with a PR interval of .24 sec right intraventricular conduction delay and left anterior fascicular block The echocardiogram was normal

Case No 2 E K a 66 year old Caucasian male was in excellent health until 1 day prior to admission when he noted left hand weakness and lightheadedness He was initially evaluated at his local hospital where electrocardiographic monitoring documented sinus bradycardia sinoatrial exit block and sinoatrial and AV Wenckebach The physical examination was normal except for an apical S_4 gallop and faint right carotid bruit The ECG revealed sinus bradycardia with episodes of sinoatrial Wenckebach a PR of .20 sec and periods of escape junctional rhythm at 50/minute The chest x ray outlined a normal cardiac silhouette

Case No 3 P R a 52 year old Caucasian female with rheumatic valvular disease had undergone aortic and tricuspid valve replacement 21 months prior to admission Her postoperative course was complicated by the development of a mediastinal hematoma and asymptomatic sinus bradycardia ranging from 50 to 60/minute Six months prior to admission she noted recurrent palpitations described as a regular tachycardia often occurring with near syncopal symptoms The admission physical examination revealed the PMI 13 cm lateral to the mid sternal line prosthetic S_1 and S_2 a Grade II/VI systolic ejection murmur heard at the apex and second right intercostal space and Grade I/VI early diastolic murmur at the left sternal border Electrocardiograms showed broad notched P waves sinus bradycardia with a PR of .20 sec nonspecific ST and T changes as well as occasional junctional escape rhythm at 38/minute In patient monitoring documented paroxysmal atrial tachycardia. The chest x ray showed mild left ventricular enlargement and prosthetic aortic and tricuspid valves

Results

Electrophysiologic data from patient R M documented markedly prolonged intra and inter atrial conduction times with high to low right atrial conduction interval of 94 msec (normal ≤ 48 msec)[1] and right to left atrial interval of 110 msec (normal ≤ 60 msec) The majority of the corrected sinoatrial recovery times were normal in the range of 270 to 330 msec though probable 2 1 and 4 1 sinoatrial exit block occasionally occurred following termination of atrial pacing and resulted in a few corrected recovery times of 1130 to 2450 msec Sinoatrial conduction times were prolonged and ranged from 200 to 290 msec (normal ≤ 205 msec)[3] Before pharmacologic intervention occasional junctional escape beats occurred after rapid atrial pacing without retrograde atrial depolarization resulting in atrial standstill for up to 4.9 sec (Fig 1) Antegrade AV

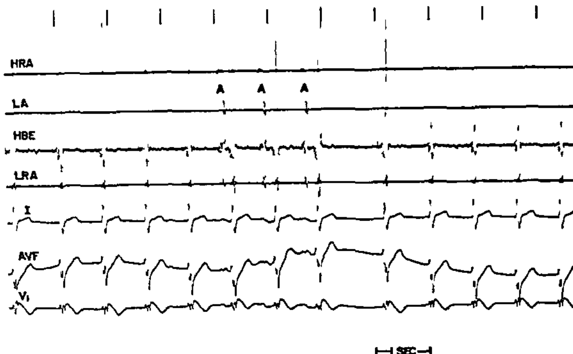


Fig. 2. Junctional rhythm with prolonged atrial standstill post procainamide is interrupted only rarely by atrial activity demonstrating dissociation and then interference.

conduction was not demonstrably impaired with an AH interval of 120 msec and 1:1 AV conduction up to an atrial pacing rate of 133/minute. However, the HV interval was prolonged at 58 msec (normal < 55 msec.). Following 500 mg of procainamide administered intravenously over 10 minutes the HV interval lengthened to 70 msec while atrial conduction time and AH interval remained essentially unchanged. Striking suppression of sinoatrial activity occurred with the appearance of junctional rhythm and complete retrograde VA block lasting approximately 10 minutes. During this time atrial standstill existed except for rare spontaneous atrial depolarizations initiated by fragmented right atrial activity (Fig. 2). Atrial pacing at the same stimulus threshold was still easily performed. However, right atrial activity progressively fragmented during atrial pacing and atrial latency and interatrial Wenckebach now occurred with high right atrial pacing at a rate of 188 (AA – 265 msec.) compared to 1:1 atrial capture at 226/minute (AA – 320 msec.) prior to procainamide (Figs. 3 and 4). Periods of sinus rhythm then resumed interrupted by occasional junctional escape beats still accompanied by retrograde block.

Patient E. K. demonstrated spontaneous sinoatrial and AV Wenckebach during the electrophysiologic study. Intra- and interatrial conduction times were at the upper limits of normal with high right to low right atrial and right to left atrial intervals of 40 and 50 msec, respectively. Wide variability in calculated sinoatrial recovery and conduction times was noted with corrected recovery times as long as 4 630 msec with only one recovery time < 200 msec and sinoatrial conduction times ranging from 20 to 520 msec. Impaired AV node conduction was apparent with AV Wenckebach block occurring at an atrial pacing rate of 94/minute though the baseline AH interval was normal (105 msec.). Infra-nodal conduction was normal as evidenced by an HV interval of 40 msec. Occasional junctional escape beats following rapid atrial pacing elicited no retrograde atrial activity. The administration of atropine 1.5 mg intravenously over 2 minutes resulted in prolonged junctional rhythm (81/minute) with 1:1 VA conduction. AV Wenckebach block was not seen until an atrial pacing rate of 120/minute. The addition of propranolol 5 mg intravenously over 2 minutes elicited AV dissociation with interference and occasional high grade sinoatrial exit block post atrial pacing. The resulting junctional rhythm again elicited no

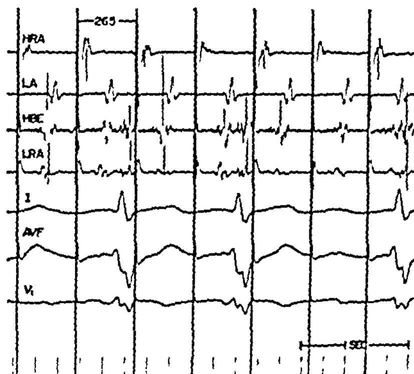


Fig 3 In patient R M prior to procainamide 1 1 atrial capture continued at an atrial pacing rate of 226 minute (AA – 265 msec)

retrograde VA conduction This yielded periods of atrial silence of up to 4 6 sec (Fig 5)

Atrioventricular dissociation occurred throughout the atrial pacing study of patient P R Right to left atrial conduction was normal at 38 msec Corrected sinoatrial recovery times were prolonged in the range of 430 to 1 190 msec while sinoatrial conduction times were also increased at 200 to 490 msec Transient atrial tachycardia was frequently provoked with rapid atrial pacing In one instance the spontaneous termination of atrial tachycardia resulted in 4 1 seconds of asystole which was interrupted by a junctional escape rhythm lasting 10 4 seconds during which total atrial silence was present (Fig 6) Following 1 0 mg of atropine intravenously junctional rhythm prevailed with occasional sinus beats only rare retrograde VA block was seen Antegrade AV conduction was normal with Wenckebach block occurring at an atrial pacing rate of 146/minute

Discussion

Temporary atrial standstill is most difficult to detect from the surface electrogram and is rarely seen during electrophysiologic investigation Sinoatrial dysfunction is necessary however were the sinoatrial region the only area of functional abnormality, retrograde atrial depolarization should occur In his report of patients with chronic sinoatrial heart block Rasmussen[1] noted that retrograde P waves were found in most cases when sinus node activity had failed and AV nodal rhythm supervened In addition ectopic atrial foci might also be expected to intervene when established atrial silence occurs due to retrograde VA block These three patients (see above) constitute a spectrum of severity of conduction system disease Yet all of them demonstrated multiple sites of conduction system impairment which enabled this seemingly unstable phenomenon of atrial electrical silence to occur despite continued response to external stimuli

All patients exhibited sinoatrial node disease and periods of atrial standstill without acute drug intervention although patient P R was receiving maintenance digoxin at the time of the study The longest period of spontaneous atrial standstill (14 5 seconds) occurred in this patient The other two patients showed dramatic atrial suppression necessitating junctional rhythm after the administration of procainamide and propranolol respectively

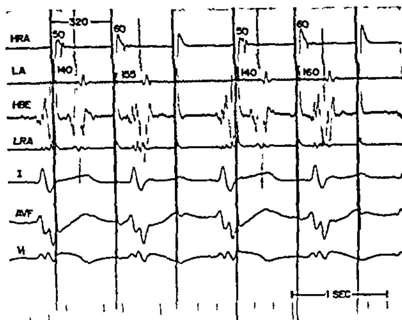


Fig 4 Post procainamide in patient R M., right atrial latency increased and interatrial Wenckebach occurred at a pacing rate of 188/minute (AA – 320 msec.) Latency from stimulus artifact to right atrial depolarization increased from 50 to 60 msec with a concomitant increase of 140 to 155 msec to left atrial depolarization The third stimulus artifact failed to capture the atria

The atrial effects of procainamide in patient R M are unusual in view of the extensive electro physiologic studies showing the major effect of procainamide to be on the infranodal conduction system [1] Therapeutic intravenous doses of procainamide consistently produced 17 to 19 per cent HV prolongation while AV conduction was only minimally involved if at all in these studies Sinus rates in man showed 0 to 7 per cent increase with one notable exception reported by Schein man and associates a patient with pre-existing episodes of sinus bradycardia developed further sinus slowing progressing to junctional rhythm with 1 1 retrograde VA conduction (procainamide concentration 7 mcg /ml) However dog studies have shown up to 20 per cent slowing in sinus rate post procainamide Microelectrode techniques have revealed that procainamide produces no significant change in phase 4 depolarization of sinoatrial cells this supports the usual clinical findings Procainamide does increase the effective refractory period of the atrium and recent studies have shown a significant increase in atrial conduction times following procainamide In patient R M procainamide profoundly sup pressed the sinoatrial region and atria Atrial activity was absent for fully ten minutes except for rare spontaneous depolarizations and periodic exogenous atrial pacing Though measured intra and inter atrial conduction times were essentially unchanged atrial conduction was impaired during atrial pacing Whereas the baseline atrial following rate was 226/minute after procain amide atrial Wenckebach occurred at 188/ minute The exact site of this conduction delay is uncertain but even local delay at the pacing site was evidenced by progressive fragmentation of the right atrial activity This phenomenon lends support to the concern expressed by Scheinman and colleagues [9] regarding the administration of procainamide to patients with sinus bradycardia or significant atrial conduction disease though in their patient 1 1 VA conduction prevented atrial standstill

Propranolol exacerbated baseline sinoatrial disease in patient E K producing periods of marked sinoatrial exit block or sinoatrial arrest As opposed to procainamide suppression suppres sion of spontaneous sinoatrial node depolariza tion rate is expected with beta blockade but not to this degree Propranolol suppression of atrial automaticity apparently inhibited ectopic atrial pacemakers as well

In the presence of intact atrial excitability

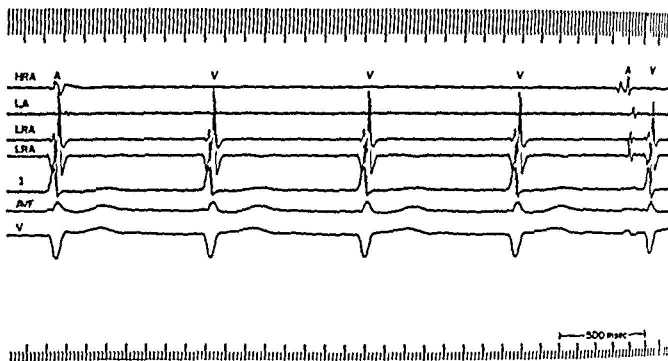


Fig. 5. Patient E. K. demonstrated junctional rhythm with atrial standstill (2.9 seconds) and occasional spontaneous but fragmented right atrial depolarizations post propranolol. Although a His bundle potential was not clearly recorded at this time, the QRS morphology did not change with atrial conducted beats.

atrial standstill is not due to dysfunction of the sinoatrial node and atrial muscle alone. Junctional rhythm with retrograde atrial capture would be expected; therefore, AV node and/or infranodal disease must be concurrent. Although Akhtar and associates found AV conduction to be better than VA conduction in 36 of 50 patients studied when His bundle deflections were found during ventricular pacing, the AH interval was similar to the HA interval. These investigators found 11 of the same patients demonstrating retrograde block. However, none demonstrated atrial standstill.

Apart from the marked atrial degeneration found in one patient, Rosen and co-workers described diffuse pathologic changes in two patients with atrial standstill consisting of arteriosclerosis, focal fibrosis and fibroelastosis in the perinodal regions, junctional tissue, and bundle branches, though only one had HV prolongation. The electrophysiologic data in our patients would be compatible with these described pathologic lesions. Patients E. K. and P. R. exhibited retrograde block within the AV node. Patient E. K. had obvious AV node disease with baseline impairment of antegrade and retrograde conduction which was partially reversed by atropine and markedly worsened post propranolol. This demonstrated autonomic influence suggests that the block occurred within the AV node region. Patient P. R., on the other hand, had no evidence of impaired antegrade AV node conduction, yet demonstrated significant retrograde VA block, again near abolition of the retrograde block after atropine suggests block in the AV nodal region. The response of patient R. M. to procainamide incriminates the infranodal region—very likely the high junctional region since a His bundle potential preceded each QRS with a prolonged HV interval of 70 msec. Antegrade AV conduction in this patient appeared to be normal, making retrograde AV node block less likely, but not impossible as shown by patient P. R. We cannot exclude extreme atrial refractoriness as the cause of the observed retrograde block, but this seems unlikely as the total explanation since atrial pacing with capture at the same stimulus threshold was easily performed during the time of atrial standstill. Increased atrial refractoriness, however, may play a contributory role as suggested by Waldo and associates.

The possibility of sino-ventricular conduction in patient R. M. cannot be entirely excluded since extensive right atrial searching for isolated

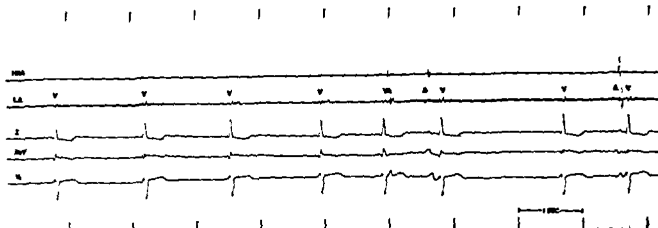


Fig 6 Transient atrial standstill occurred post spontaneous termination of atrial tachycardia in patient P R Ventricular depolarization is also reflected in the left atrial electrograms however this is clearly not left atrial depolarization as can be seen during the fifth ventricular complex when spontaneous atrial activity occurred

electrical activity was not performed However the rare spontaneous atrial depolarizations that occurred during the period of standstill initiated interference with the junctional rhythm and thus were out of phase with the predominant rhythm

These patients demonstrate that temporary atrial electrical silence can be the result of extensive conduction system disease without involving drug intoxication hyperkalemia infarction or an immediate postoperative status Previous conclusions that lack of atrial responsiveness is the cause of temporary atrial standstill appear not to be universally valid These three patients with intact atrial excitability nevertheless manifested temporary atrial silence because of the coexistence of sinoatrial and atrioventricular conduction disease Consequent loss of atrial transport may further increase the symptoms of bradycardia in these patients and if prolonged might encourage mural thrombus formation with subsequent embolization Certainly prior concern about procainamide administration to bradycardia subjects is well founded

Summary

Temporary atrial standstill is a relatively rare event requiring intraatrial electrogram recordings for its documentation Previous reports have emphasized its relationship to drug intoxication infarction the immediate post open heart surgery period or the premorbid state significant impairment of atrial excitability is usual The occurrence of atrial standstill in the presence of intact atrial excitability suggests electrical isolation of the atria The three patients we describe manifested temporary atrial standstill while maintaining atrial excitability Diffuse conduction system disease and drug effects played a contributory role

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Transmural myocardial infarction with "normal" coronary arteries

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All of the well documented causes of transmural myocardial infarction are known to be related to stenosis of the coronary arteries or rarely to anomalous development of the coronary system. With the advent of coronary angiography it became apparent that there was a group of patients with myocardial infarctions (MIs) who had no significant angiographically apparent coronary stenosis. The concordance of myocardial infarction and unobstructed arteries was subsequently observed in several patients at postmortem examination. The diagnosis of myocardial infarction with normal coronary arteries (MI & NCA) has been applied to these patients in whom no significant anatomical narrowings could be found to explain the presence of myocardial infarction.

Though patients with MI & NCA represent only a small fraction of patients with myocardial infarction, an understanding of this experiment of nature may shed light on the pathogenesis of *myocardial infarction. Thus it was felt appropriate* to compile the reported cases of this syndrome according to uniform criteria and to analyze their clinical, angiographic, and postmortem characteristics. Furthermore, since a number of hypotheses have been advanced to explain this disorder, a critical review of the evidence supporting the various proposals is in order.

Methods

Proudfit, Shirey, and Sones found two cases of MI & NCA in 176 patients with ECG evidence of antecedent myocardial infarction who subsequently underwent coronary angiography. However, in one of these patients the QRS changes of his myocardial infarction disappeared in one month. Bruschke and associates[6] reported a 4 2 per cent prevalence of non obstructive coronary artery disease in patients undergoing coronary angiography who had had documented MIs. Khan and Haywood[7] found nine cases in 78 consecutively catheterized patients status post myocardial infarction, a prevalence of 11 per cent. Despite the relatively high prevalence reported by these authors, less than 100 patients with myocardial infarction and normal coronary arteries have been reported. The true prevalence of MI & NCA is difficult to estimate because patients with MIs are not all routinely catheterized and those who succumb do not all have their coronary arteries carefully examined. No doubt young patients with MIs are more apt to be studied because MIs occur less frequently in these patients *and physicians may be more diagnostically and* therapeutically aggressive with this age group. Thus the prevalence figures of Proudfit and colleagues, Bruschke and co-workers, and Khan and Haywood[7] are more likely to be high than low.

Since non specific ECG changes in the ST and T waves may accompany chest pain of various etiologies and because valvular heart disease and coronary angiography itself may have played a role in many cases of MI & NCA, the following criteria were adopted to select cases for review:

1 History consistent with acute myocardial infarction.

2 Transmural myocardial infraction by serial electrocardiogram, vectorcardiogram, or by autopsy examination.

3 Transient elevation of cardiac enzymes compatible with MI.

4 Patent coronary arteries by angiography or autopsy examination.

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Table I Transmural myocardial infarction with normal coronary arteries—clinical data

Author/data	Age/sex	ECG Location of MI	Interval from MI to cath (autopsy)	Risk factors				
				DM	Lipid	Cig	HBP	FH
Campeau et al 1968	2[illegible] M	AWMI	[illegible]½ mo	–	–	?	–	–
	32 M	ILWMI	[illegible] mo	–	–		?	–
Bruschke et al 1971	33 F	AWMI	[illegible] mo	–	–	?	–	?
	43 M	ASMI	51 mo	–	–	?	–	
	29 M	IWMI	[illegible] mo	–	–	?	–	?
Clancy et al 1971	34 F	AWMI	29 mo	–	–	+	–	–
	3[illegible] F	AWMI	6 mo	–	–	+	+	+
Dear et al 1971	43 M	IWMI	16 mo	?	?	?	?	?
Nizet et al 1971	17 M	IWMI	3 [illegible] mo	–	–	–	–	–
Kimbiris et al 1972	24 M	PLWMI	26 days	–	–	–	–	–
	16 M	ASMI	3 mo	–	–	–	–	–
Fotts et al 1972	28 M	ILWMI	4 mo	–	–	?	–	?
	28 M	ASMI	[illegible] yr	+	+	?	–	+
Schatz et al 1973	14 M	ILWMI	1 mo	–	–	–	–	–
Khan et al 1974	43 M	AWMI	6 Weeks to 6 months	–	–	+	–	–
	45 M	ALWMI		–	–	–	–	–
	49 M	IWMI		–	–	+	–	–
	31 M	IWMI		–	–	+	–	–
	22 M	ALWMI		–	–	+	–	–
	[illegible] M	Apical		–	–	+	–	–
	30 M	IWMI		–	–	+	–	+
	37 M	AWMI		–	–	+	–	–
	34 M	Apical		–	–	+	–	–
Brest et al 1974	3[illegible] M	ILWMI	3 mo	–	–	?	–	–
	3[illegible] M	ILWMI AWMI	5 mo., (13 mo.)	–	–	?	?	–
	40 M	ILWMI	6 mo	–	–	?	–	–
	28 M	ILWMI	5 mo	–	–	?	?	?
	38 M	ILWMI	6 mo	?	?	?	–	–
Elliot et al 1974	4[illegible] M	ASMI	(12 days)	?		?	+	?
Regan et al 1975	36 M	AWMI	2.5 mo	–	–	+	–	?
	59 M	AWMI		–	–	+	–	?
	54 M	AWMI		–	–	+	–	?
	34 M	IWMI		–	–	+	–	?
	49 M	AWMI	(?)	–	–	+	–	?
	[illegible] M	IWMI	(?)	–	–	+	–	?
	46 M	IWMI	(?)	–	–	+	–	+
Eslami et al 1975	[illegible]2 F	IWMI	3 mo	–	–	–	–	–
	27 M	ILWMI	3 mo	–	–	–	–	–
	2[illegible] M	ALWMI	9 mo	–	+	+	–	–
	2[illegible] M	IWMI	4 mo	–	–	–	–	–
	18 M	ALWMI	4 mo	+	–	–	–	+
	28 M	IPWMI	19 mo	–	–	+	–	–
	24 M	IWMI	3 mo	–	+	+	–	–
	45 M	IWMI	48 mo	–	?	+	–	

? = Information not published ASMI = Anteroseptal MI AWMI = Anterior wall MI ALWMI = Anterolateral wall MI IWMI = Inferior wall MI ILWMI = Inferolateral wall MI IPWMI = Inferoposterior wall MI

Chest pain before MI	*Chest pain after MI*	*Recurrent MI*	*Comments*
No	Yes	Extended day 16	Rigid slowly emptying diag br Diff Poor contraction
No	No	?	
No	No	No	Fusiform LAD aneurysm 36 weeks pregnant
?	Yes	No	
?	Yes	No	
No	Yes	No	Oral contraceptives
No	No	No	11 days post partum
Yes	Yes	No	3 40% lesions in LAD
No	No	No	
Yes	No	No	Thrombocytosis
No	No	No	Anomalous origin LCA from R sinus of Valsalva
No	Yes	No	
No	Yes	No	Marked periph vasc disease
No	Yes	No	
?	*6 patients with recurrent* chest pain post MI	No	
?		No	
?		?	
?		No	
?		No	
?		No	
?		No	
?		No	
?		No	
No	No	No	
No	No	Yes died	Alcohol abuse
No	No	No	
No	No	No	
Yes	Yes	No	
?	–	Died acutely	
No	?	?	Alcohol abuse
No	?	?	
No	?	?	
No	?	?	
?	–	Extended MI died	
?	–	Extended MI died	
?	–	Died acutely	" "
?	No	No	Oral contraceptive until 6 mo prior to MI
?	No	No	
?	No	No	
?	No	No	MI 2 days after industrial exposure to nitroglycerin
?	No	No	
?			Vent tachycardia 10 mo after MI
?	No	No	
?	Yes	No	CVA preceded MI

Table I Continued

Author/data	Age/sex	ECG location of MI	Interval from MI to cath (out pt)	Risk factors				
				DM	Lipid	Cig	HBP	FH
Ciraulo 19	40 F	ASMI AWMI	?3 mo	−	+	+	−	+
Sasse et al 197	16 F	IWMI	3 ½ mo	−	−	−	−	−
	26 F	ASMI	4 mo	−	−	+	−	−
Chesler et al 19	32 M	ILWMI	2 mo	−	−	+	−	−
Croen et al 1976	41 M	AWMI	(wk)	−	−	−	−	−
Rosenblatt et al 19	32 M	AWMI	4 wk to 3 mo	−	+	+	−	+
	32 M	AWMI		−	−	+	−	+
	26 M	AWMI		−	−	−	+	+
Johnson et al 19	24 M	High lat. WMI IWMI AWMI	? mo 21 mo	−	−	+	+	−
Michaelson et al 19	39 M	ILWMI × 2	2 yr 10½ yr	−	−	−	−	−
Oliva et al 19	44 M	LWMI	12½ hours	−	−	−	−	−
	36 M	IWMI ALWMI	3½ hrs 11½ hrs	−	−	+	−	−

5 Acute event unrelated to coronary angiography

6 Absence of clinically important natural or prosthetic valvular heart disease

Fifty six patients were found in the literature who satisfied the above criteria

Review of literature

The 56 patients who met the above criteria are a heterogeneous group who demonstrate some striking features detailed in Table I and summarized in Table II The mean age is 33 8 years for males (range 14 to 59 years) and 29 6 years for females (range 16 to 40 years) There is a marked male preponderance with 49 men and only seven women reported All but one woman in Table I had a concomitant condition that has been associated with hypercoagulability

Chest discomfort either typical exertional chest pain or atypical pain was noted to have occurred in only seven patients (12 per cent) prior to the acute myocardial infarction Patients with transmural MI & NCA do not have a uniformly good prognosis even over the relatively short follow up periods reported Recurrent MI occurred in 9 per cent and cardiac death occurred in 12 per cent of patients reviewed Thirty six per cent of patients continued to have chest pain at times after their MI

The presence or absence of one or more of the major coronary atherosclerosis risk factors (diabetes, hyperlipidemia cigarette smoking hypertension family history of myocardial infarction) was mentioned in all patients though each factor was not specifically noted in every case report Nevertheless there was a remarkable lack of multiple risk factors in these patients none had four risk factors while only eight patients had two or three risk factors Twenty four had one risk factor and the remainder 24 patients, had no risk factors noted The most commonly noted factor was cigarette smoking present in patients

Discussion

Though myocardial infarction with normal coronary arteries is a subject of numerous case reports and editorials the etiology of this syndrome remains unknown The major areas of speculation include abnormality in hemoglobin-oxygen dissociation anomalous coronary circulation misinterpretation of coronary angiograms small vessel disease coronary thrombosis or embolism with recanalization and coronary artery spasm The evidence in favor of each of these hypotheses will be discussed separately

Hemoglobin-oxygen dissociation Eliot and Bratt[x] compared hemoglobin-oxygen dissociation curves in 15 premenopausal women with previous MIs or positive exercise ECG and

Chest pain before MI	Chest pain after MI	Recurrent MI	Comments
No	Yes	Yes	Oral contraceptive × 2 weeks
No	No	No	36 weeks pregnant
Yes	No	No	30 weeks pregnant
No	No	No	Mitral valve prolapse
?	?	Died	Marathon runner
Yes	No	No	
No	No	No	
No	No	No	
No	Yes	Yes	
Yes	Yes	Yes	
No	?	?	
Yes	Yes	Yes died	

normal coronary angiograms with 15 apparently healthy women They found the ischemic group to have curves shifted to the right Unfortunately the control women were not matched for risk factors and were not evaluated for the presence of ischemic heart disease themselves Several of the ischemic women had ECG changes and chest pain with hyperventilation alone Despite these objections and many others three patients who died had subendocardial myocardial infarctions at autopsy No transmural MIs were observed however

Vokonas and colleagues studied 15 patients with angina and arteriographically normal coronary arteries and found hemoglobin-oxygen dissociation curves that were indistinguishable from controls However none of Vokonas patients had sustained myocardial infarctions and only three had positive stress tests Thus his patients may not be comparable to those of Eliot and Bratt

It may be concluded then that abnormal hemoglobin-oxygen dissociation is as yet an unproven mechanism for the production of transmural myocardial infarction

Anomalous or aneurysmal coronary arteries Myocardial infarction occurs not uncommonly in patients with congenitally abnormal coronary circulation Anomalous origin of the left coronary artery from the pulmonary artery or from the anterior sinus of Valsalva are mentioned in this respect Congenital or acquired aneurysms of the coronary arteries may develop thrombosis which may occlude the lumen or embolize distally Kimbiris and colleagues discussed a 16 year old male patient who suffered an acute transmural anteroseptal MI and whose catheterization three months later revealed normal coronary arteries except for anomalous origin of the left coronary artery from the right sinus of Valsalva Bruschke and co workers[a] reported a 33 year old woman in her 36th week of pregnancy who had an acute transmural anterior wall MI and whose catheterization five months later showed patent coronary arteries and a fusiform aneurysm of the proximal left anterior descending artery Although these cases are reported as MI & NCA the coronaries were not in fact normal Thus a definitional question exists as to whether these patients should be grouped with those of MI & NCA

Misinterpreted angiograms James has suggested the unpopular notion that patients with MI & NCA do have obstructive disease of the large coronary arteries but that their coronary angiograms did not demonstrate it Coronary angiography is known to underestimate occlusive coronary disease compared to pathologic examination James personal observations support this assertion and led him to conclude that the most frequent explanation for angina without

Table II. Clinical characteristics of 56 patients with transmural myocardial infarction and normal coronary arteries

Age		
Men	33.6 yrs.	(14-[illegible])
Women	29.6 yrs.	(16-40)
Sex		
Men	49	(8[illegible])
Women	7	(12%)
Antecedent chest pain	7	(12%)
Chest pain following MI	20	(36%)
Recurrent MI	3	(5%)
Cardiac death	7	(12%)

coronary disease is an incorrect interpretation of the coronary angiograms.

Possible errors in interpretation include: (1) failure to visualize parts of the coronary arteries which contain significant disease; (2) occlusion of a branch vessel at its origin from the parent vessel so that dye is not seen in the branch; (3) occlusion of a major vessel with development of radially arranged collaterals around the occlusion—this "starburst" effect may be misinterpreted as normal; and (4) a partially occluded vessel with a slit-like lumen may appear unobstructed if viewed in only one plane.

Even expert angiographers will on occasion fail to demonstrate significant coronary narrowings, but it is unlikely that this is the major explanation for MI & NCA. In the six cases of transmural MI & NCA who died acutely, autopsy demonstrated no significant coronary artery disease. This indicates that at least in these patients, the syndrome of MI & NCA does exist.

Coronary thrombosis with lysis or recanalization. After Herrick's 1912 description of the clinical features of acute coronary occlusion, coronary thrombosis became synonomous with MI. However, autopsy studies later made it apparent that MI sometimes occurred in the absence of autopsy demonstration of coronary thrombosis. The absence of thrombotic occlusion at autopsy suggested either that thrombosis had no part in the acute occlusion or that clot lysis occurred prior to the patient's death. The same consideration has been postulated in several cases of MI & NCA. Of course, if a thrombosis were demonstrated by coronary angiography following an acute MI and a subsequent angiogram showed complete resolution, the case would not be strictly considered an MI & NCA.

In 1973 Henderson and colleagues reported a demonstration of complete resolution of an obstructing coronary lesion. A 34-year-old woman with a six year history of oral contraceptive use suffered an acute anterior wall MI. Coronary angiography seven and one-half months later demonstrated a smooth fusiform 50 per cent narrowing of the left anterior descending coronary artery which was absent without residual wall abnormality during repeat angiography 39 months post myocardial infarction. This was felt to represent the course of a coronary thrombosis with gradual resolution.

As discussed earlier, six women in Table I with normal coronary arteries and transmural MI had coexisting states which have been associated with hypercoagulability. Three were pregnant, one was 11 days post partum, and two were using oral contraceptives. The seventh woman had discontinued oral contraceptives six months prior to her MI. Oral contraceptives have been anecdotally associated with MI and coronary thrombosis among women. The Coronary Drug Project found an increased incidence of serious non-fatal cardiovascular events in men treated with high-dose estrogen. In contrast, Vessey and Doll found no increased prevalence of oral contraceptive use in women 16 to 40 years of age with MI. Waxler and associates have suggested that estrogens may retard atherosclerosis but predispose to coronary thrombosis in the rare susceptible patient.

If coronary thrombosis with lysis is the mechanism which causes myocardial infarction with angiographically normal coronary arteries, then lysis and resolution must occur prior to the angiogram. Weisse and co-workers studied the time course of resolution in dogs by inserting an electrically tipped catheter into a coronary artery. Thrombosis induced by passing electrical current through the catheter tip took 30 to 60 days to resolve. Henderson and associates' case of a 34-year-old woman with probable coronary thrombosis took between seven and one-half and 39 months to resolve.

In light of this information, it is informative to examine the time interval from myocardial infarction to catheterization in patients reported as MI & NCA. Until recently, the shortest interval reported was 26 days, with most cases having catheterization delayed several months or more. However, Oliva and Breckinridge have recently reported two patients who underwent coronary angiography within 12 hours of the onset of

symptoms of their MI with one angiogram being done three hours and 45 minutes after the onset of symptoms In neither case were angiographic abnormalities found which could explain the extent of MI though distal occlusions were noted on the catheterizations These findings could be explained in one of two ways (1) a mechanism other than coronary thrombosis may cause MI & NCA or (2) thrombotic occlusion may dissolve more rapidly than the three hours and 45 minutes that it took to perform angiography following the onset of symptoms Thrombotic occlusions which rapidly lyse and embolize distally may account for the large infarctions noted and the seemingly trivial distal occlusions

Platelet thrombi are known to occur and may lyse much more rapidly than fibrin thrombi perhaps in minutes[41] Mustard and associates[41] have produced myocardial infarctions in experimental animals by infusion of platelet aggregates Jørgensen and colleagues[4] have produced MI in pigs by infusing adenosine diphosphate a known platelet stimulator into the coronary artery Haerem[4] has found that patients who died suddenly of cardiac causes have increased size and number of platelet aggregates in their epicardial arteries though the differences from controls were not highly significant Steele and co workers[16] noted decreased platelet survival in eight patients with MI & NCA though there was considerable overlap with patients with MI and coronary atherosclerosis Salkey and Dugdale[47] had previously found decreased platelet survival in three patients with MI & NCA

One case in the literature of MI & NCA demonstrates a relation with thrombocytosis Kimbiris and colleagues reported a 24 year old man with an episode of chest pain and transient ECG changes which were followed three months later with an acute transmural posterolateral MI Platelet count was noted to be 645 000 Coronary angiograms were normal 26 days post MI

Coronary embolism Embolism to the coronary arteries is a well recognized etiology of MI and occurs with various clinical conditions valvular heart disease mural thrombus endocarditis prosthetic valve implant cardiac catheterization atrial myxoma etc The prevalence of coronary artery embolism in autopsied patients with myocardial infarction has been estimated to be as high as 13 per cent

Several cases of MI & NCA have occurred in patients who had had predisposing causes for embolization[8, 4] but angiography demonstrated either normal angiogram or angiogram consistent with embolization with subsequent resolution It would not be unreasonable then to suggest as Arnett and Roberts have done[5] that many patients reported as MI & NCA have had embolic MI with resolution of the emboli prior to angiography However few of the patients in Table I had conditions associated with embolization

Small vessel disease Some have suggested that disease in vessels too small to be resolved on coronary angiography accounts for transmural MI & NCA Small vessel disease is known to occur in patients with various systemic syndromes such as progressive systemic sclerosis[51] However the clinical characteristics of these patients are far different from patients with MI & NCA[52] Systemic disease is almost invariably concomitant with small vessel disease of the heart and is always absent in patients with transmural MI & NCA In small vessel disease the heart is usually enlarged while in transmural MI & NCA it is most often normal in size Small vessel disease of the heart is associated with a high incidence of arrhythmias conduction disturbances and syncope while patients with MI & NCA have no arrhythmias before the acute episode and seldom after recovery from the MI Patients with small vessel disease have nonspecific ST T wave changes but normal QRS complexes on their ECGs while those with MI & NCA have evolving transmural or nontransmural MI Last and most convincing patients with small vessel disease have histologic evidence of small vessel involvement at autopsy Patients who have died of transmural MI & NCA have had no evidence of small vessel involvement Thus it may be concluded that small vessel disease is unlikely to play a significant role in the pathogenesis of transmural MI & NCA

Spasm of the coronary arteries Spasm of the coronary arteries has been unequivocally demonstrated to cause myocardial ischemia in Prinzmetal s or variant angina About 35 per cent of patients with variant angina have angiographically normal coronary arteries while the remainder have varying degrees of atherosclerosis[53] Selzer[53] found no overlap between patients with variant angina without demonstrable coronary artery disease and myocardial infarction Nevertheless there are a few patients with angiographically patent coronary arteries reported who may well have had spasm play an important role in their

MIs Johnson and Detweiler[30] reported a follow up on a patient previously reported by *Sidd and associates*[31] *This was a 21 year old man with* three MIs over 21 months *and multiple episodes* of severe chest pain once with *documented ST* elevation but *no* infarction *An angiogram* performed with ergonovine *maleate showed* coronary artery spasm and ST elevation Seven weeks *after the angiogram* the patient suffered his third *MI Its FCG location* was in the same distribution as the ST segment elevations noted during angiography

Cheng and co workers reported *a case of a* 52 year old woman who during *catheterization* showed spasm of the left circumflex *artery at the* level of the obtuse marginal branch *The appearance* of the occlusion was most *suggestive of* spasm The patient went on to *evolve an inferior* wall MI Repeat catheterization *done* three months later showed normal *coronary arteries* Another piece of evidence to support *the hypothesis* that MI & NCA may be *induced by spasm is the case reports by Lange and* associates He described rest angina MIs *sudden death* and normal coronary *angiograms in* patients who were periodically *withdrawn from* chronic industrial exposure to *nitroglycerin* A *well documented case of MI & NCA following* withdrawal from industrial *exposure* to nitroglycerin is reported by *Eslami and colleagues*

Spasm *and platelet* thrombosis have been *proposed to act in a self* perpetuating cycle to cause *myocardial infarction* with normal coronary *arteries* *Spasm may result in intimal* damage which causes platelet *aggregation Platelets* then release various *potent vasoactive* substances such as *prostaglandin G* *thromboxane* A_2 or serotonin which *reinforce and prolong* spasm Alternatively platelet *aggregation* may be the initiating event *leading to spasm*

Coronary spasm *may be caused by catheter* manipulation and *has certain characteristics* which allow *differentiation from* spontaneous coronary spasm *However the anatomic demonstration of spasm requires angiography and it is* currently *not possible to prove unequivocally* that catheterization *is causally unrelated* Nevertheless *Maseri and co workers* have presented *convincing evidence that spasm of extramural coronary arteries plays a role* in unstable angina in patients with normal or atherosclerotic coronary *vessels* and that many of these patients go on to develop MI

Conclusion

The syndrome of transmural myocardial *infarction* with normal coronary arteries is an *unusual condition occurring* in probably less than *one or two per cent of patients* with MI although *the prevalence has been reported to be* as high as *11 per cent These figures* are prone to overestimation *because of* patient selection and because *of the relatively long intervals* between the acute *event and catheterization*

The vast majority of patients are *men* with a *male female ratio of 7 to 1* It is of interest to note *that while women predominate* in the syndrome *of angina with normal coronary arteries* men *are far more likely to actually* have MIs with *normal coronary arteries* Furthermore since all *but one of the women* with transmural MI & *NCA were either pregnant* post partum or *taking oral contraceptives it would be* tempting *to implicate these factors* in the women with MI *& NCA No such common thread could be* found *in the men*

The relative youth of patients with MI & NCA (mean age men 34 years women 30 years) compared with those with MIs due to atherosclerosis probably reflects both the association of atherosclerosis with advancing age and a tendency to perform angiography in young patients with MIs The observation that only 14 per cent of those with *MI & NCA had* two or more risk *factors* for atherosclerotic coronary artery disease correlates with the absence of significant atherosclerosis in these *patients*

The typical patient with MI & NCA is a young man with few if any risk factors or more unusually a young woman under the hormonal *influence of pregnancy* or oral contraceptives In most cases (88 per cent) there has been no prior history of chest pain and the patient is likely to be free of pain after his MI Prognosis for short term follow up is good However there are enough atypical patients with MI & NCA so that certain caveats must be added Antecedent chest pain does not eliminate MI & NCA from consideration A large number of patients (36 per cent) have recurrent chest pain following *MI and* a smaller but significant number reinfarct (9 per cent) and/or die (12 per cent) The latter complication rate is no doubt underestimated because of the lack of long term follow up on the majority of reported cases

The etiology of MI & NCA has not been determined The evidence supporting *abnormal*

hemoglobin-oxygen dissociation as an etiology is far from strong and this hypothesis has long awaited confirmation Misinterpretation of coronary angiograms certainly cannot explain all cases of MI & NCA since several cases have been reported with autopsy observations Small vessel disease is an unlikely explanation both on clinical and pathological grounds

The typical case of MI & NCA may be best explained by a single chance event such as a coronary embolism or thrombosis Resolution of the coronary occlusion would occur prior to catheterization in these cases This theory fails to explain atypical features found in many cases such as prodromal chest pain post infarction pain and recurrent infarction In these cases coronary spasm perhaps in concert with platelet aggregation best accounts for clinical presentation and course

Though very early coronary angiography may reveal important clues as to the pathogenesis of MI & NCA the development of non invasive methods for visualizing the coronary circulation may be necessary to elucidate the mechanism of myocardial infarction in the presence of normal coronary arteries It may well be that the name of this syndrome only reflects our inability to detect coronary occlusion early in the course of myocardial infarction in these patients

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Observations on unstable angina pectoris with particular respect to management

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In recent years a great deal of attention has been focused on a small but distinct group of patients with ischemic heart disease who experience prolonged bouts of chest pain at rest accompanied by electrocardiographic changes of myocardial ischemia but without any objective evidence of myocardial necrosis. Opinion is divided regarding the prognosis and the optimal management in this situation.[5]

Contrary to previous beliefs,[6] it has become apparent that the prognosis of patients within the group as defined above, at least in the acute phase, is relatively benign. There is no definite evidence available about the superiority of medical or surgical treatment.[5,1] Consequently a shift in emphasis from acute intervention to a more elective form of surgical therapy has taken place.[1] In a majority of patients bed rest and beta adrenoceptor antagonists have been sufficient to relieve symptoms completely and have led to rapid stabilization.[3,7,2]

Beginning in November 1975, we established a protocol of treatment to study the response prospectively in a group of patients after precise clinical definition. Coronary angiography was performed routinely in all patients. The following report concerns 70 such patients who have now been followed for a mean duration of twenty months (range 4 to 36 months).

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Patients and methods (Table I)

Between the period November 1975 and July 1978, 70 patients (58 men and 12 women) with a mean age of 55 years (range 34 to 70) were admitted to our coronary care unit who met the following clinical criteria:

1. Repeated typical chest pain at rest lasting for more than 15 minutes with little relief afforded by nitrates and needing frequently parenteral opiates for relief from pain. These episodes of pain could be appearing for the first time or could be superimposed on already established angina pectoris.
2. Changing patterns of ST and T wave changes on the electrocardiogram.
3. No enzymatic evidence of myocardial necrosis (creatine phosphokinase, aspartate transaminases, and lactate dehydrogenase repeated at least three times during the first twenty-four hours).

Coronary arteriography. Once an infarct was excluded, coronary arteriography and ventriculography was performed within 48 to 72 hours of admission following Judkin's technique in all patients. Both major coronary arteries were filmed in multiple projections including craniocaudal projection. Narrowing of the lumen of one or more branches of the coronary arteries of 75 per cent or more was described as critical. If a significant occlusion was present, a second lesion was considered significant if there was a luminal narrowing of 50 per cent or more. The patients were grouped according to the number of vessels involved—i.e., one, two, or three vessel disease. The left ventricle was opacified in the 30 degree

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Table I *Clinical details of patients with unstable angina pectoris*

	Group I	*Group II*	*Group III*	*Group IV*	*Group V*
Number of patients	36	5	17	11	5
Mean age (years)	[illegible]4 (36–[illegible]0)	51 [illegible] (4[illegible]–[illegible]1)	5[illegible] (47–67)	5[illegible] 3 (48–[illegible])	51.2 (34–[illegible])
Previous angina pectoris	10	2	3	5	0
Old myocardial infarction	9	1	5	8	0
Cardiomegaly	3	1	1	4	0

Table II Hemodynamic and angiographic findings in patients with unstable angina pectoris

	Group I	*Group II*	*Group III*	*Group IV*	*Group V*
Number of patients	36	5	17	11	5
LVEDP 14 mm Hg	36	4	17	4	5
LVEDP 14 mm Hg	–	1	–	–	–
Ejection fraction >50	32	4	11	1	5
" " 25–50	4	1	1	4	–
" <25	–	–	–	4	–
Ventriculography I	12	2	2	–	5
II	22	2	11	4	–
III	2	1	–	7	–
IV	–	–	1	2	–
Angiography					
1 vessel RCA	8	–	–	–	–
LAD	11	2	4	1	–
" CX	1	–	–	–	–
2 vessel RCA + LAD	9	1	1	2	–
RCA + CX	1	–	–	–	–
LAD + CX	4	–	3	–	–
3 vessel RCA + LAD + CX	2	2	3	–	–
Main stem single	–	–	1	–	–
" + RCA + LAD + CX	–	–	1	1	–

right anterior oblique view. The left ventricular end diastolic pressure was measured through fluid filled catheters (Cook's pigtail). A pressure above 14 mm Hg was considered abnormal. The ejection fraction was calculated by the area-length method. In cases of aneurysm no ejection fraction was measured.

The ejection fraction was classified as normal (above 50 per cent), reduced (25 to 50 per cent) and severely reduced (below 25 per cent). The segmental contraction abnormalities were assessed visually. The abnormalities of contraction pattern were arbitrarely divided into four groups:

Group 1 = normal
Group 2 = localized hypo- or akinesia
Group 3 = globally reduced contraction pattern
Group 4 = aneurysm

Protocol of treatment (Fig. 1). The patients were observed in the coronary care unit. Soon after the diagnosis was established based on clinical features and coronary angiography all the patients received intensive medical treatment. Those with main left coronary artery lesions formed the only exception. They were scheduled for coronary bypass graft surgery during the acute phase. The medical treatment consisted of bed rest, propranolol HCl (Inderal) in sufficient dosage to achieve a resting heart rate below 60 beats per minute, nitrates when necessary, and anticoagulants. The latter were discontinued when the patients were fully ambulant. Response to medical therapy determined the future management. Those patients who remained symptomatic were operated electively two to three weeks after the trial with medical therapy. Those who became symptom free were discharged and were followed at three monthly intervals. During the follow up surgical treatment was again considered if there was a recurrence or progression of angina pectoris.

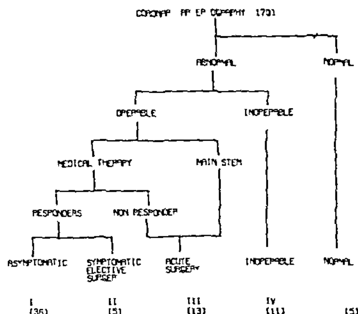


Fig 1 Flow diagram indicating management of patients with impending myocardial infarction. Numbers of patients in parentheses

Table III Clinical course of the patients with unstable angina pectoris

	Group I	*Group II*	*Group III*	*Group IV*	*Group V*
Number of patients	36	5	13	11	5
Mean follow up period (months)	23 5 (4 36)	21.5 (12 26)	17.3 (9-36)	23 6 (5-36)	18 1 (10-31)
Operative mortality	–	0	0	–	–
Perioperative infarction	–	1	1	–	–
Angina pectoris	8	1	2	8	0
New myocardial infarction	3	0	1	1	0
Sudden death	1	0	1	3	0
Living	35	5	12	8	5
NYHA class 1	27	4	10	0	5
2	8	1	2	3	0
3	0	0	0	5	0
4	0	0	0	0	0

Results (Figs 2 to 4 and Tables I to III)

Coronary arteriography and ventriculography were performed in all patients Complications were limited to two episodes of ventricular fibrillation Both patients were instantly defibrillated successfully In one patient with persistent chest pain electrocardiographic and enzymatic evidence of myocardial infarction was observed six hours after completion of the investigation

Clinical course Angiographic findings and the response to the therapy were discriminant enough to allow division of the patients into five groups

Group I This group comprised 36 patients (52 per cent) who became rapidly symptom free on medical treatment Two of these patients however developed acute myocardial infarction within the first week of admission During the follow up period no recurrence or progression of symptoms was observed Ten patients had previous angina pectoris Nine patients had a history of healed myocardial infarction In three patients cardiomegaly was demonstrated on chest x ray films.

LV ANGIOGRAPHY LVEDP was normal in all the patients Ejection fraction was normal in all except four where it was reduced The LV

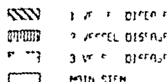
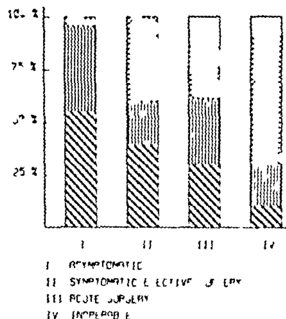
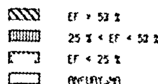



Fig 2 Bar graph illustrating angiographic findings in the four groups of patients



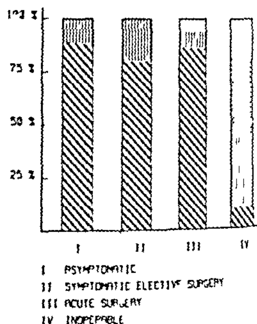


Fig 3 Bar graph illustrating per cent ejection fraction (EF) in the four groups of patients.

contraction pattern was normal in 12 patients 22 patients showed localized hypokinesia or akinesia In two patients globally poor contraction of the left ventricle was observed

CORONARY ANGIOGRAPHY In 20 patients one vessel disease was involved In four of the eight cases with RCA involvement this vessel was totally occluded Two patients had three vessel disease while the rest had two vessel disease with LAD disease in nearly all the cases

FOLLOW UP Despite adequate response to medical treatment non fatal myocardial infarctions developed in two patients during the period of admission One of these infarctions occurred within 6 hours after angiography Two months after discharge one patient died suddenly This patient had normal left ventricular function and localized stenosis of the left anterior descending artery There was one non fatal myocardial infarction during follow up

Out of 35 survivors 27 patients are completely symptom free while eight patients have persistent but mild anginal symptoms which are adequately controlled by beta blockers and which do not interfere with their everyday activities

Group II This group consisted of five patients (7 per cent) who responded adequately to medical therapy initially however due to the recurrence of severe angina pectoris they were operated within 2 to 6 months after coronary arteriography Two patients had previous angina pectoris and one patient showed cardiomegaly One of the patients had a previous history of myocardial infarction

LV ANGIOGRAPHY In only one patient the LVEDP was more than 14 mm Hg Four patients had a normal ejection fraction while in one patient this was reduced Two patients had a normal left ventricular contraction pattern Two patients showed only localized hypokinetic areas One patient showed globally poor contraction of the left ventricle

CORONARY ARTERIOGRAPHY Three vessel disease was demonstrated in three patients in one patient two vessels were involved while two patients showed involvement of the left anterior descending artery only

FOLLOW UP There was no operative mortality nor any incidence of perioperative myocardial infarction During follow up all the patients are

living four are symptom free while one patient has mild anginal complaints This one patient received three saphenous vein bypasses only one of which was open at reinvestigation

Group III This group comprised 13 patients (18 per cent) who did not respond to medical therapy in the acute phase It includes two patients with critical left main coronary artery lesions and 11 patients who had prolonged bouts of chest pain despite adequate medical treatment Three patients had previous angina pectoris Five patients had a history of previous myocardial infarction One had signs of cardiomegaly

LV ANGIOGRAPHY The LVEDP was normal in all patients Ejection fraction was normal in 11 patients while in one it was reduced Two patients had normal left ventricular contraction pattern 11 patients had localized hypokinesia or akinesia and one patient had an apical aneurysm

CORONARY ARTERIOGRAPHY There was a demonstrated left main coronary artery lesion in two patients one of these patients had a lesion in all the vessels In four patients the LAD was the only vessel involved In four patients two vessel disease was found and in three patients three vessel disease was seen

FOLLOW UP There was no operative mortality while in one patient a perioperative myocardial infarction was documented During follow up of the surviving patients ten patients are symptom free while two patients continue to have mild anginal symptoms which are adequately controlled by beta adrenergic blocking agents and nitrates Two months after bypass surgery one patient sustained an acute myocardial infarction Repeat angiography showed closure of all the bypass grafts There was one sudden death two months after operation (one bypass LAD) Two patients after operation have persistent anginal symptoms in one patient the grafts are open in the other patient both grafts are closed

Group IV This group comprised 11 patients (16 per cent) who on the basis of coronary arteriography and LV angiographic findings were considered to be inoperable Five patients had previous angina pectoris Eight of the patients had sustained a myocardial infarction and four patients demonstrated cardiomegaly on chest x ray

LV ANGIOGRAPHY In seven patients the LVEDP was higher than 14 mm Hg in two more

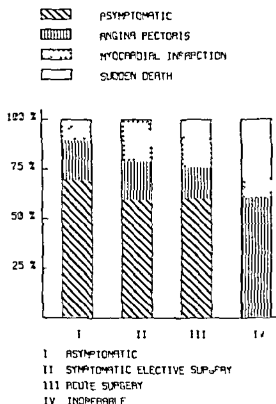


Fig 4 Bar graph presenting follow up percentages in the four groups of patients Patients were followed for a mean of 22 months with a range of 4 to 36 months.

it was higher than 20 mm Hg The ejection fraction was severely reduced in four patients and normal in one patient Ventriculography demonstrated generalized hypokinesia in seven patients in four a localized hypo or akinesia and in two patients an anterolateral aneurysm

CORONARY ARTERIOGRAPHY Arteriograms revealed three vessel disease is seven patients two vessel involvement in two patients three vessel disease and severe left main coronary artery lesion in one patient and one vessel disease (LAD) in one patient

FOLLOW UP During the acute phase none of the patients went on to myocardial infarction During the follow up period three patients have died suddenly Of the eight surviving patients five continue to have moderately severe anginal symptoms and two patients have associated left ventricular failure adequately controlled with treatment One patient sustained a *non fatal* myocardial infarction

Group V This group comprised five patients (7 per cent) who on coronary arteriography were found to have normal coronary arteries and left

ventricular function In two of these patients coronary artery spasm was demonstrated during pain on arteriography In two patients signs consistent with cardiomyopathy were observed In one patient no immediate explanation of signs and symptoms was apparent, however a routine cholecystography in this patient revealed multiple stones in the gall bladder After cholecystectomy the patient has become symptom free and manifests a disappearance of electrocardiographic changes

Discussion

Unstable angina pectoris is the presently preferred term to describe all the patients who occupy a twilight zone between classical acute myocardial infarction and exercise induced angina pectoris For over 40 years this clinical syndrome has been reported regularly under a variety of names impending acute coronary artery occlusion intermediate coronary syndrome acute coronary insufficiency status anginosus impending myocardial infarction and pre infarction angina—each one implying varying degrees of urgency and foreboding in terms of treatment and prognosis respectively In the studies reported before 1970 a high acute infarction rate (21 to 80 per cent) and mortality rate (up to 60 per cent) were observed but important differences in the clinical presentation of the series of patients described lack of precise diagnostic criteria and an ever changing pattern of medical management makes it difficult to draw any useful conclusion about the natural history of the clinical syndrome as a whole Besides the last decade has seen several interventions in the natural history of ischemic heart disease which preclude reference to the previous observations Thus widespread dissemination of knowledge through the media about the gravity of chest pain with consequent rapid hospitalization and intensive monitoring in the coronary care units has led to early recognition of patients at high risk The early institution of optimal medical therapy in the shape of nitrates beta adrenoceptor antagonists and antiarrhythmic agents has contributed significantly to a reduction in early morbidity and mortality

As a direct consequence a number of studies which appeared during the 1970s registered a sharp drop in the acute myocardial infarction rate as low as 5 to 10 per cent and a low mortality rate during the acute phase of unstable angina pectoris These studies also emphasized the heterogeneity of the patient population which led Conti and colleagues[11] to try to distinguish several subgroups so as to allow the study of natural history in real perspective and at the same time permit proper comparison of treatment

The cohorts which became easily recognizable were

1 Patients with angina pectoris of recent onset

2 Changing pattern in patients with stable angina pectoris

3 Angina at rest

Of course there could be a considerable overlap between the three groups thus Group 3 patients may or may not have had anginal symptoms previously The adverse prognostic significance of persistent pain history of previous myocardial infarction and angina pectoris was also stressed

Perhaps the greatest impact has been made by the safe use of coronary arteriography Precise anatomical characterization of the coronary arterial tree not only establishes the severity of the obstructive coronary artery disease but also identifies patients who have either no demonstrable coronary atherosclerosis or those with critical left main coronary artery stenosis Left ventricular angiography and the related hemodynamic parameters give essential information about left ventricular function Both the severity of obstructive coronary artery disease and left ventricular dysfunction have a significant influence on the prognosis and management of unstable angina pectoris In the majority of the series where angiography was done routinely the presence of extensive coronary atherosclerosis in patients with unstable angina was confirmed The distribution of arterial abnormalities was similar to that found in patients with stable angina pectoris Of particular interest was the fact that 5 to 10 per cent of the patients were invariably found to have normal or minimally diseased arteries in all studies

In the late 1960s the advent of myocardial revascularization added an extra dimension to the management of ischemic heart disease Naturally one of the earliest targets for surgical therapy were patients who presented with unstable

angina pectoris This was on the assumption that the clinical syndrome of unstable angina pectoris was a harbinger of acute myocardial infarction and possibly of sudden death At least on theoretical grounds the surgical intervention was advocated to bring about reduction in the morbidity and mortality rates Enthusiasm for acute operative treatment was also generated by the favorable outcome in a small number of patients reported[34, 36] However several comparatively large scale studies albeit uncontrolled showed that surgical therapy at least during the acute phase[4] was not without appreciable risk

Evidence gathered from the recently reported series [21] provided the platform to launch our own study It soon became apparent that despite the favorable response to medical therapy described in these series all the patients were operated eventually The natural history of medically treated patients was available only where the patients had either refused operation or were inoperable[1, 3] In the only series where an attempt was made to treat all patients medically 70 per cent of the patients were operated because of unacceptable angina pectoris The results of the latter study might give the impression that the majority of patients with unstable angina pectoris are more likely to have persistent anginal symptoms despite optimal medical therapy Yet the entire series of these patients had a previous history of angina pectoris and 50 per cent had sustained myocardial infarction in the past—the risk factors which have been shown to adversely affect the course and prognosis of the clinical syndrome of unstable angina pectoris[26] In our own study we decided to follow up prospectively a series of carefully selected patients with rest angina where intensive medical therapy formed the primary basis in the management Surgical intervention would be considered only if the medical had failed in relieving symptoms and in cases of left main coronary artery stenoses

The importance of coronary angiography in this respect cannot be overemphasized We were fully cognizant of the potential risks[1, 3] involved but on the basis of available evidence we realized that coronary arteriography performed early in the course of the syndrome was mandatory to the future management In our series the investigation was done without any fatal incident It provided us with the framework on which to base our policy of future management Thus patients with substantial left main coronary artery disease were operated acutely This group of patients has been shown to respond unfavorably to medical treatment and may have an improved prognosis if operated early[3, 7] Seven per cent of the patients were found to have normal coronary arteries which finding has regularly been reported in all other series also All the other patients operable and inoperable were offered intensive medical treatment initially We believe that coronary angiography in expert hands is safe and does not carry any extra risks The risks such as they are may have to be taken in those very patients where precipitate action is warranted either because of persistent symptoms or the presence of life threatening obstructive lesions[1, 1, 9]

Symptoms The symptoms conform to the experience of others 82 per cent of the patients in our series became rapidly symptom free on medical treatment and only 18 per cent were operated within the first week of admission either because of persistent symptoms or because of left main coronary artery lesions Another 7 per cent were electively operated within six months of admission because of the recurrence of symptoms under optimal medical treatment During a maximal follow up period of three years (range 4 to 36 months) 27 patients remain asymptomatic on medical treatment Eight patients in Group I continue to have symptoms although they are controlled adequately with treatment Analysis of the arteriographic abnormalities in the latter group of patients demonstrated either isolated left anterior descending artery stenosis or multiple vessel disease None of the patients with isolated right coronary artery disease have persistent symptoms The majority of patients treated surgically are symptom free Only three patients out of 18 continue to have mild symptoms which can be explained entirely by the graft patency

Myocardial infarction Among the medically treated group 6 per cent of the patients sustained a new myocardial infarction within the first year of admission Among the surgically treated group two patients developed perioperative infarction and one patient sustained a new infarction within three months of operation (4 per cent) Recatheterisation in the latter revealed closure of all the grafts The number of patients in both groups are too small to allow any statistical comparison

Mortality In the medically treated group four patients died (6 per cent) but three of these patients had severe left ventricular dysfunction and were therefore considered inoperable In the surgically treated group there was no operative mortality rate (0 per cent) but one patient died suddenly two months after operation

Medical vs surgical treatment Although no comparison of the two treatments is implied in our study there are several points which are worthy of comment In the first instance the majority of patients during the acute phase became quickly symptom free on medical treatment in common with the experience of others Secondly the declining trend in the morbidity rates in patients on medical treatment is confirmed in the present study[1] Finally surgical treatment in properly selected cases can be undertaken with acceptable risk and a good clinical result

Considerable support for these findings has been provided by the publication of the National Cooperation Study Group on unstable angina pectoris in which have been obtained in a large series of randomized patients treated medically and surgically

Finally the results of this study allow us to make the following conclusions

1 Coronary angiography played an important role in the diagnosis prognosis and management in this group of patients

2 Prognosis was relatively benign in patients with mild to moderately severe coronary sclerosis

3 The majority of the patients responded rapidly to medical therapy and an appreciable number have stayed symptom free

4 Surgery acute or selective was required in about 25 per cent of the patients

Summary

Seventy patients with a diagnosis of unstable angina pectoris were admitted They met the following criteria (1) repeated typical chest pain at rest lasting for more than 15 minutes (2) changing patterns of ST and T wave changes on the electrocardiogram and (3) no evidence of myocardial necrosis

In all patients coronary arteriography was performed within 48 to 72 hours after admission without any untoward effects All patients received intensive medical treatment bed rest propranolol and nitrates when necessary Response to this treatment determined the future management Those patients who remained symptomatic during the acute phase and those with left main coronary artery stenosis were operated within two or three weeks after the treatment with medical therapy Those who became symptom free were followed up at three monthly intervals Surgical treatment was offered if there was a recurrence or progression of angina pectoris Those who were inoperable and those with no detectable abnormalities on the angiogram were also followed up regularly

With intensive medical therapy 82 per cent of the patients became symptom free only 18 per cent were operated either because of persistent symptoms or because of left main coronary artery lesions During follow up however another 7 per cent were operated electively because of the recurrence of symptoms despite adequate medical treatment

Among the medically treated group 6 per cent sustained a new myocardial infarction while among the surgically treated group two patients developed a perioperative infarction and one patient sustained a new infarction during follow up (4 per cent) Four patients in the medically treated group (6 per cent) died but three of these patients were considered inoperable In the surgically treated group there was no perioperative mortality one patient died suddenly two months after surgery

It is concluded that the majority of patients with unstable angina become rapidly symptom free on medical therapy following the trend observed during the last decade Coronary angiography performed early is essential for dictating future management Surgery if required can be undertaken safely on an elective basis

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Surgical treatment of anomalous left coronary artery from pulmonary artery Follow-up in teenagers and adults*

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Before surgical therapy was available the Bland White Garland (B W G) syndrome was marked by short life and sudden death[1] In this syndrome an anomalous left coronary artery arises from the pulmonary artery (ALCAPA) Blood flows to the myocardium from the aorta through a right coronary artery which arises normally Survival depends greatly on the extent of collateralization between the right and anomalous left coronary artery Operative attempts to improve oxygen saturation in the blood of the aberrant vessel began with unsuccessful efforts by Potts using an aortico pulmonary window Poudrage pulmonary artery banding ALCAPA ligation as well as left common carotid artery and left subclavian artery grafting to the abnormal left coronary artery have been tried A technique which appears physiologically more promising is ligation of the ALCAPA at the pulmonary artery ostium by sutures and simultaneously grafting from the aorta to the left coronary artery with Dacron or a saphenous vein graft (SVG) Reimplantation of the anomalous vessel into the aorta is an alternative technique first used in repair of the anomalous right coronary artery from the pulmonary artery but applicable to ALCAPA as well Follow up reports suggest the value of surgical repair

The purpose of this study is to compare postoper- ative results of ALCAPA ligation alone with simultaneous ALCAPA ligation and aorta to left coronary artery saphenous vein grafting.

Method

A search principally of the published English language medical literature was conducted Additional cases were sought randomly by correspondence with the directors of cardiac catheterization laboratories at several major medical centers All patients who were included had been diagnosed by angiography as having an anomalous left coronary artery from the pulmonary artery during life In order to obtain a relatively physiologically homogeneous group we arbitrarily required that all were age 13 years or more at diagnosis All patients reported in the literature since the description of the syndrome or discovered by correspondence were included in the study if they met the above criteria and had received either ALCAPA ligation alone (Group A) or ALCAPA ligation and simultaneous aorta to ALCAPA saphenous vein grafting (Group B) Patients were excluded from this study if they had ligation and vein grafting at separate operations if a prosthetic mitral valve was inserted or if the ALCAPA was reimplanted in the aorta Patient entrance into the present study ended July 31 1976

By correspondence with the current health care provider the following information was requested concerning each patient patient's initials month and year of birth sex month and year diagnosis established month and year of surgery type of surgery none ligation ligation and saphenous vein graft other month and year of last follow

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Table I Follow up data on patients with anomalous left coronary artery from pulmonary artery diagnosed during life at age 13 years or older

Pt no	Ref no	Year birth	Sex	Age at diag (yrs)	Date of surg	Type surg	Date last reported	
							Alive	Death
1	23	39	M	16	Aug 55	E	Mar '77	
					Aug 68	L + G		
2	24	45	F	17	Oct 6?	L	Aug '77	
3	25	48	M	18	66	L	Feb '71	
4	26	'21	F	45	Oct 66	L	May '77	
5	27	4?	F	23	Mar 66	L	Jan '75	
6	27	19	M	47	Aug 66	L		68SD
7	28	51	M	15	Jul 67	L	Aug '77	
8	28	39	F	27	Nov 67	L	Nov '75	
9	29	43	M	22	Aug '65	L	Sep '77	
10	30	27	M	41	May 68	L		Nov '73SD
11	31	48	M	20	Dec 67	L + G	'75	
12	32	'26	F	39	Mar 66	L		Jan '73SD
13	33	41	F	27	Feb 68	L	Jan '77	
14	34	'35	F	34	Mar 69	L + G	May '77	
15	35	'25	F	46	Aug '71	L + G	Aug '77	
16	PC	40	F	30	Mar '70	L + G	'77	
17	36	'37	M	29	Jul 66	L + G	May '77	
18	37	51	F	22	'73	L + G		At operation
19	38	'34	F	42	Mar 76	L + G	Mar '78	
20	PC	'25	F	46	Sep 71	L + G	Aug '73	
21	39	'28	F	45	Nov 73	L + G	May '77	
22	39	54	F	13	Sep '74	L + G	May '77	
23	40	49	F	15	64	L	May '77	
24	41	47	M	26	Oct '73	L + G	May '77	
25	PC	37	M	35	'72	L + G	Jul '77	
26	PC	57	M	13	Mar 71	L + G	Sep 77	
27	42	'21	F	50	29Nov72	L + G	Apr '78	
28	43	35	F	42	Feb 7	L + G	Jul 77	
29	44	40	F	23	Jan 64	L	'76	

Abbreviations E = expl red L + G = ligation & saphe us vein graft SD = sudden non accidental death L = ligation nly PC = personal mmunication.

up clinical condition at last follow up (presence or absence of angina pectoris shortness of breath easy fatigue congestive heart failure New York Heart Association Classification of symptoms preoperatively and postoperatively patency of saphenous vein graft if restudied circumstances of death and autopsy reported if death had occurred)

The statistical method used to compare the groups was the generalized Wilcoxon test for arbitrarily singly censored samples described by Gehan[2]

Results

Twenty nine patients who met the study criteria were identified from seven countries (Table I) Four cases had not been reported previously Follow up was obtained on all The female to male ratio of 1 6 to one agrees with other reports

Table II presents data on patients receiving ligation alone Group A The mean age at last follow up was 37 ± 9 4 years the mean postoperative period was 9 2 years There were no operative deaths Late sudden death occurred in three patients 2 years (Case 6) 5.5 years (Case 10) 6 8 years (Case 12)

Case 6 New Zealand—His physician reported the man died suddenly and non accidentally two years after ALCAPA ligation No autopsy was performed

Case 10 Osaka Japan—Ligation of ALCAPA at its origin in 1968 In December 1971 he was admitted and treated for four months because of heart failure and developed a pulmonary embolus Medication was digitalis diuretics and anti

Table II Group A Ligation only postoperative follow up results teenagers and adults with ALCAPA No operative deaths

Pt no	Age at last report (yrs)	Survival post-op (yrs)	Preop signs & symptoms	NYHA class		Remarks Postop signs/symptoms
				Preop	Postop	
2	3[illegible]	1[illegible]	Heart murmur	II	II	PVC ACP ND X2
3	[illegible]6	8				
4	56	10 6	A	III	I	Rest I
5	33	8 8	Excessive fatigue	III	I	Mild MR, unchanged
6	49	1	ACI	II		SD '73
7	26	10 1	Heart murmur	I	I	
8	36	8	Mild fatigue HM	II	I	
9	34	12 1	Heart murmur	I	I	
10	4[illegible]	5 5	A SOB Ht size	III	II	SD Nov '73
12	47	[illegible] 8	A DOE HM	III	II	SD Jan '73
13	36	8 9				
23	28	13	HM	I	I	ACP PML +ETT
29	36	1[illegible]	HM	III	II	
Mean	37	9 2				
ST D	9 4	3 [illegible]				

Abbreviations A = angina pectoris ACP = atypical chest pain DOE = dyspnea on exertion ETT = exercise tolerance test HM = heart murmur MR = mitral regurgitation ND = normal delivery NYHA = New York Heart Association I = palpitations PML = prolapse mitral leaflet PVC = premature ventricular contraction SD = sudden non accidental death SOB = shortness of breath ST D = standard deviation.
Also includes suturing ALCAPA ostium in pulmonary artery

coagulant Since the spring of 1973 his condition had been relatively good and he performed light work such as flower culture until his death He was found on the road in the afternoon of 22 November 1973 He looked well and not unusual on that morning and his wife was not at home when he died The autopsy was not performed

Case 12 Austin Texas—Ligation was performed in March 1966 Her husband described her sudden death 6 8 years later She was moving into a new home and seriously planning on saphenous vein graft in the near future as her physician had recommended While carrying packing boxes from her car to the house she became short of breath without angina Moments later he found her lying apneic and unresponsive at the foot of the stairs She died before an ambulance arrived No autopsy was performed

Table III presents data for Group B patients The mean age at last follow up for Group B was 38 ± 11 3 years not significantly different from Group A The female to male ratios were comparable for both groups The average survival after operation was 4 8 ± 2 9 SD years for Group B Preoperative signs and symptoms were characteristic[3 4 1] Symptomatic improvement in about half of Group A and Group B patients was reflected by their change in New York Heart Association Classification

For Group B (Table III) one intraoperative (Case 18) and no late deaths occurred among 1[illegible] cases Eleven of 14 (78 per cent) restudied soon after surgery had technically good grafts One graft was occluded (Case 1) and two revealed graft stenosis (Cases 20 and 27) Postoperative classical angina and palpitations occasionally occurred with functional grafts (Cases 14 19 an[illegible] though one graft (Case 20) was stenotic at time of study

Postoperative systolic and diastolic murmurs were noted with technically excellent surgical results in Cases 17 19 and 27 Marked decrease in the size of the right coronary artery postoperatively was noted in Cases 19 22 and 25

There was no significant difference in the probabilities of survival for Groups A and B when compared by singly censored samples and by life table analysis The comparisons were made for slope for each year and for cumulative years (Fig 1) The value of Gehan s W statistic was –1[illegible] with a standard error of 23 46 The asymptomatic Z score of – 60 was not statistically significant at the 05 level

Discussion

Corrective coronary artery surgery appears to be the most reasonable choice for patients with an anomalous left coronary artery arising from the

Table III Group B Concomitant ligation or ostial occlusion and saphenous vein graft only postoperative follow up results teenagers and adults with ALCAPA operative death included

Pt no	Age at last rept (yrs)	Survived postop (yrs)	Preop main symptoms	NYHA class		Postop coronary angio				Postop signs and symptoms
				Preop	Postop	Yes /no	Patent graft	Graft to cor anastomosis	PO	
1	38	9 1	HM DOE	I	I	Yes	No	Occluded	4 yr	None
11	27	8	P,S HM A EKG	II	I	Yes	Yes	Good		
14	41	8 2	NDX3 P HM SOB A	II	II	Yes	Yes	Good	1 mo	P,A depressed
15	52	6	AEKG AETT	I	I	Yes	Yes	Good	7 mo	None
16	37	7	A DOE	II	I	No				Freq bronchitis
17	40	10 8	HM A P	II	I	Yes	Yes	Good	7 yr	†
18	22	0	HM DOE NDX3, A P	III						Operative death
19	43	1.5	A HM SOB	III	II	Yes	Yes	Good	6 mo	A,SOB † P
20	48	1 9	HM	I	II	Yes	Yes	Stenosis	2 yr	A
21	49	3 5	P SOB A	III	I	Yes	Yes	Good	8 mo	
22	23	2.8	C HM	I	I	Yes	Yes	Good	2 wk.	
24	30	3 5	HM A P	II	I	Yes	Yes	Good	3 mo	Well carpenter
25	40	5 0	A	II	I	Yes	Yes	Good		
26	17	3.5	HM	I	I	Yes	Yes	Good		None
27	57	5 5	SOB A	III	II	Yes	Yes	80% stenosis		†
28	43	0 5	HM A 60% LAD NDX1	II	I	Yes	Yes	Good	1 wk.	DM
Mean	38	4 8								
ST D	11 3	2 9								

Abbreviations A = angina pectoris ACP = atypical chest pain AEKG = abnormal electrocardiogram AETT = abnormal exercise tolerance test C = cyanosis DM = diastolic murmur DOE = dyspnea on exertion HM = heart murmur MR = mitral regurgitation ND = normal delivery NYHA = New York Heart Association P = palpitations PML = prolapse mitral leaflet PO = postop PVC = premature ventricular contraction S = syncope SD = sudden death, n neonatal SOB = shortness of breath ST D = standard deviation

Decrease in size of RCA postoperative †Systolic and diastolic murmur postoperative

pulmonary artery Without surgery death in infancy is frequent Sudden death in those who survived to young adult life is also characteristic Several follow up studies suggest surgery may prolong life

From the present study there is no observed difference in probability of postoperative survival for Group A and Group B patients Three late sudden deaths in Group A may eventually prove to be significant since there have been no late deaths reported so far in Group B patients Grafts appear to remain patent at late study postoperatively though perhaps less frequently than grafts performed for atherosclerotic coronary artery disease

A report by Anthony and co workers[5] causes concern Sudden death occurred in a ten year old female who had late graft closure subsequent to a technically satisfactory ligation plus saphenous vein graft This patient was excluded from entry into our study by age at time of diagnosis Had she been included the slight difference in trend between Groups A and B would become even less significant Angina and associated arrhythmias persisting after successful surgery in Group A may have led to ventricular fibrillation and therefore may have contributed to the sudden deaths described above These findings when present are therefore of great concern in Group B as well

This study has many limitations The study population was arbitrarily limited to those who have survived to teenage years or beyond in hope of obtaining a group of patients which was relatively homogeneous (i.e with sufficient collaterals to survive infancy and have only Class I to III symptoms) The rarity of such patients demands that the study be done retrospectively in an uncontrolled fashion There will understandably be some variation in surgical technique and competence as well as thoroughness of follow up since patients are treated at a wide range of centers Postoperative ejection fractions would have been desirable in all patients unfortunately not all were restudied postoperatively The small number of patients discovered for study virtually defies statistical analysis since a minimum of 67 patients per group would be required to achieve

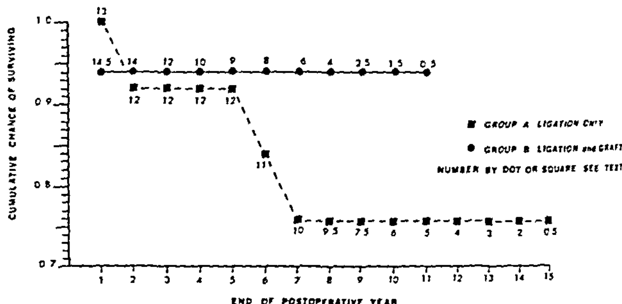


Fig 1 This figure depicts the cumulative chance of surviving surgery for both Group A and Group B patients. The number by the dot or square is the number alive and under observation at the beginning of the yearly interval minus deaths during the interval and minus half of withdrawals alive during the interval. There was no significant difference between the groups survival at any postoperative year

statistically significant difference in seven year survival at the 90 per cent confidence level if 0.74 (Group A) and 0.9 (Group B) were the expected survival rates. Clearly no such large group of patients is currently available for study. Finally the later development of combined ligation and SVG to ALCAPA dictates a shorter mean follow up for group B compared to Group A. Perhaps the data will become more significant with longer follow up as the difference in the mean follow up periods diminishes

Despite these limitations important findings arise from this study. In the teenager or adult with ALCAPA risk of sudden death is ever present despite the type of attempted surgery although there is no statistically discernable increase in survival after ALCAPA ligation or ligation and SVG there is also no worsened survival (and both groups are theoretically improved compared to historical controls) there is a trend toward improved survival with the combined operation the findings of angina and palpitations postoperatively may herald sudden death, and the appearance of systolic and diastolic murmurs postoperatively suggests an excellent technical result with torrential flow through intramyocardial sinusoids

Based upon the above we conclude that patients with ALCAPA may be reasonably subjected to either ALCAPA ligation or ligation + SVG. In view of a trend for improved survival in the latter group and considering that, theoretically those with ligation + SVG have a return toward normal physiology with restoration of dual antegrade coronary flow we suggest a likely advantage of the combined operation over simple ligation. In view of the frequency of sudden death patients with symptoms of angina or palpitations especially those who have undergone ligation alone should be strongly considered for antiarrhythmic therapy. Careful follow up as well as expansion of the study population will be required to achieve more clarity in defining the truly optimal management of ALCAPA patients

Summary

To determine which method of surgical therapy might be optimal for patients with anomalous left coronary artery from the pulmonary artery (ALCAPA) a follow up study was performed. Twenty nine teenagers and adults who had ALCAPA diagnosed during life at age 13 years or older were identified mainly by literature search. Recent follow up was obtained on all. Thirteen treated by ALCAPA ligation alone (Group A) were followed a mean of 9.2 years postoperatively (range 1 to 15 years). There was no operative mortality. Three Group A patients died suddenly a mean of five years (range 2 to 7 years) postoper-

atively Sixteen patients treated by simultaneous ALCAPA ligation and saphenous vein graft (SVG) from aorta to left coronary artery (Group B) were followed a mean of five years (range 0 to 11 years) with one intraoperative death and no late mortality

Using the generalized Wilcoxon test for single censored samples there was no significant difference in survival at any postoperative year when comparing both Groups A and B The late appearance of sudden death in three Group A patients and no late deaths in Group B patients suggests that ligation and SVG or its equivalent may be the therapy of choice

The authors wish to express to the following physicians their appreciation for assistance in providing follow up information (case No precedes cooperating physicians names) 1 S T Ong 2 N A Massih L Leight 3, J W Harthorne G S Myers 4 H F Zinnser 5 A H G Roche 6 A H Roche 7 G Houd G Vosti 8 G Houd G Vosti 9 S C Franco 10 Y Yamane 11 R Reis 12 S M King 13 H F Zinnser 14 R M Gaisor 15 C S Thomas 16 D Frasier 17 B R Chaitman 18 K Barrand 19 C Wilson et al 20 T O Gentsch 21 P K Caves 22, P K Caves 23 N S Talner 24 N Anzai 25 D Frazer 26 A Hartman 27 J Rosch 28 R Leachman 29 W Bircks

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The atrioventricular conduction system in dissecting aneurysm of the aorta

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Atrioventricular conduction disturbances are rarely considered as a serious complication in dissecting aneurysm of the aorta,[1-4] although sudden and unexplained death is not at all infrequent.[6] In fact, the occurrence of electrocardiographic changes is considered of importance in differentiating on clinical criteria between aortic dissection and myocardial infarction.[7]

On the other hand, pathological studies have shown that a retrograde dissection from a dissecting aneurysm originating in the ascending aorta is nearly always present. This phenomenon underlies the occurrence of aortic valve insufficiency, narrowing of coronary ostia, and rupture into the pericardial cavity with cardiac tamponade. However, such observations have also shown that the hemorrhage may spread into the interatrial septum and may extend into the area of specialized atrioventricular junctional tissues.[8-11]

Because of these observations, a clinicopathologic investigation has been performed of cases with dissecting aneurysm of the aorta in order to evaluate whether or not such hemorrhages may lead to conduction disturbances.

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Material and methods

The material consisted of 48 specimens of classical complete dissecting aneurysm of the aorta. The specimens were obtained from 35 males and 13 females. The age varied from 20 to 83 years with an average age of 57 years. Cause of death was cardiac tamponade in 33, hemothorax in five, pump failure in five, cerebral ischemia in two, sudden unexplained death in three. Nine patients underwent operation.

In 42 of the 48 cases (87.4 per cent) the dissection originated in the ascending aorta, while in six cases (12.5 per cent) the initial tear was present in the descending thoracic aorta distally to the origin of the left subclavian artery.

In six of the eight hearts with a grossly identifiable hemorrhage into the atrioventricular junctional area, a histologic study of the atrioventricular conduction tissues was performed. In four of these a correlation with electrocardiographic data was possible. Five hearts without such a gross evidence and with an intimal tear in the ascending aorta were taken as "controls" and were also processed for further histologic studies.

Tissue blocks were removed from the sinoatrial and atrioventricular junctional areas, respectively.[12] They were fixed in formalin, embedded in paraffin, and serially sectioned at 10 micron thicknesses. At intervals of 25 sections, 2 sections were retained and stained with hematoxylin and eosin and the elastic Van Gieson stain. Intermediate sections were stained when this was considered necessary.

Results

All 42 specimens with an intimal tear in the ascending aorta exhibited a retrograde extension of the hematoma which reached the level of the aortic sinuses. In 23 (55 per cent) the hemorrhage

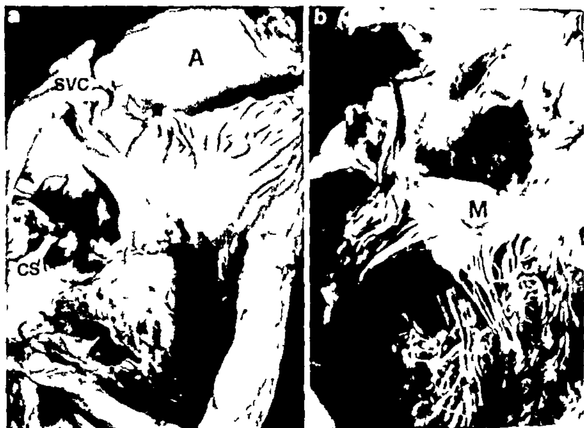


Fig 1 A and B Case 3 *A* Right side view of a typical hematoma of the interatrial septum extended to the area of the atrioventricular node *A* = aorta *CS* = coronary sinus *SVC* = superior vena cava *B* Left side view of the hemorrhagic atrial septum *M* = mitral valve

infiltrated the medial wall of the right atrium protruding into the right atrial cavity in four instances (9 per cent) and extended into the atrial septum and the coronary sinus in eight hearts (19 per cent) (Fig 1)

Among the six hearts with an intimal tear in the descending thoracic aorta there was only one which showed a retrograde dissection which extended into the ascending aorta However there was no hematoma within the atrial wall and septum in this particular case

Hematoma in the atrioventricular junctional area There were eight hearts with a grossly identifiable hemorrhage in the specialized atrioventricular junctional area The hematoma had spread from the aortic root into the base of the interatrial septum dissecting through myocardium and loosely textured fibrous and fatty tissues of the aorto atrial space The hemorrhage had spread between the transitional cell zone of the atrioventricular junction but never actually penetrated the compact node (Figs 2 and 3) Moreover the hemorrhage sometimes extended along the penetrating bundle through the central fibrous body albeit that the specialized conduction fibers themselves were never involved (Fig 2c and *d*) The branching portion of the bundle and the proximal bundle branches were never affected by hemorrhages The sinus node was normal in all instances except for one heart with an acute pericarditis in which the inflammatory process involved ganglia of the nerve plexus associated with the node In none of the five controls was there any histologic evidence for hemorrhages affecting the specialized atrioventricular junctional tissues

Clinicopathologic correlations Table I shows the correlation between the pathologic and clinical data Among the cases with hemorrhage extending into the atrioventricular junction four had electrocardiographic tracings Sinus rhythm was initially recorded in all two developed atrioventricular dissociation one developed complete heart block while one exhibited a signifi

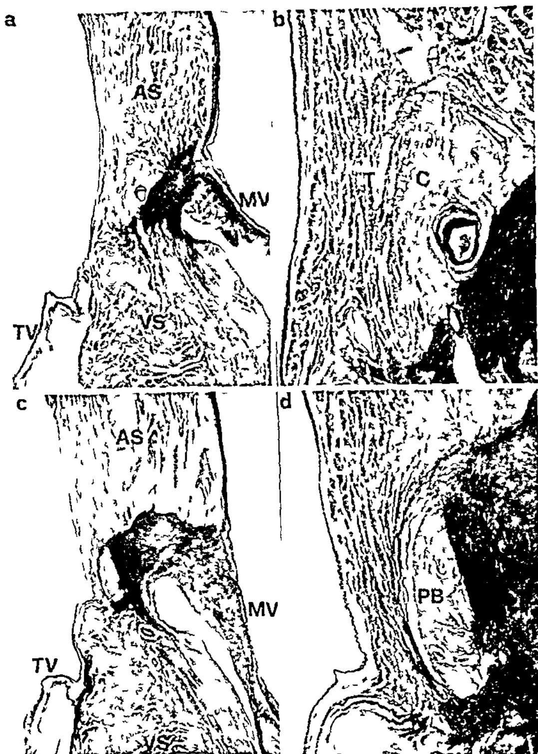


Fig 2 A through D Case 3 Histology of the atrioventricular conduction tissues. *A* and *B* The atrioventricular node the hemorrhage infiltrates the transitional zone *(T)* but spares the compact zone *(C)* *C* and *D* The penetrating bundle the hemorrhage extends along with the bundle *(PB)* but does not involve the specialized tissues (Elastic Van Gieson stain *A* and *C* original magnification ×4 *B* and *D* original magnification ×15) *MV* = antero medial mitral leaflet *TV* = septal tricuspid leaflet *AS* = atrial septum *VS* = ventricular septum

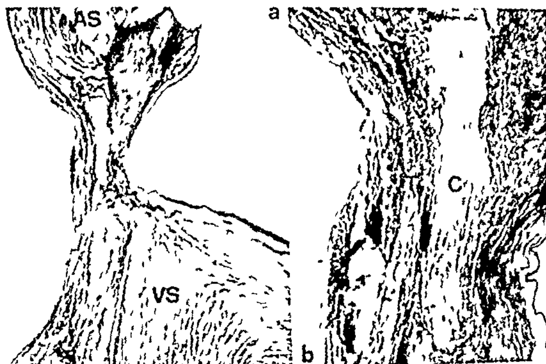


Fig 3 A and B Case 4 The histologic examination (*A* and *B*) shows the hemorrhage spreading between the *transitional cell zone (T) of the atrioventricular junctional area but sparing the compact node (C)* (Elastic Van Gieson stain original magnification (*A*) ×5 (*B*) ×30) *AS* = atrial septum VS = ventricular septum

cant prolongation of PR interval It is of interest that in one patient who initially developed atrioventricular dissociation sinus rhythm was restored shortly before death Among the controls no atrioventricular conduction disturbances were recorded

Discussion

Very little is known about atrioventricular conduction disturbances in the setting of dissecting aneurysm of the aorta Thompson in 1834[1] described a patient with a dissecting aneurysm who developed attacks of syncope alternating with episodes of an irregular pulse fluctuating between 15 and 100 beats per minute The first actual documentation of electrocardiographic evidence of atrioventricular block in the setting of dissecting aneurysm was made by Pick and Minimi the postmortem specimen showing extensive hemorrhage in the region of the atrioventricular junction Others have reported hemorrhages within the atrial septum extending into the atrioventricular junctional area

The present observations demonstrate that extension of the hematoma into the atrial septum in cases with the initial tear in the ascending aorta is not at all infrequent In eight out of f specimens with a dissection in the ascendi aorta, the hematoma had spread into the area o specialized atrioventricular junctional tis e Spread of the hematoma in this direction facilitated by the close relation between th aortic root and the interatrial septum as outline by the classical work of Burchell and Edwards When the retrograde dissection extends under neath the reflex line of the epicardium constitut ing the bottom part of the transverse sinus ea access is obtained through the aortoatrial spa to neighboring structures of which the free atria walls and the interatrial septum are the ore most directly related

It is of interest that the histologic studies re ea that the hematoma interspersed with the tra tional cell zone but did not penetrate into th core of the Tawarian system In this regard ou findings do not endorse those of Yacoub an co authors who described in four similar case massive hemorrhagic involvement of both atrio ventricular node and bundle In our opinion th hematoma and edema of the atrial septum from dissecting aneurysm is obviously more liable to disrupt the loose atrionodal connections than a

Table I

Case	Sex	Age	ECG		Survival	Cause of death	Gross anatomy	Histology	
			Admission	Later				Sinus node	AV junction
1	M	3[illegible]	Sinus rhythm	AV dissociation	50 days	Sudden	Hematoma atrial septum AV node area	Inflammation nerve ganglia	Hemorrage transitional zone
2	F	61	Sinus tachy cardia	AV dissociation Sinus rhythm again	9 days	Operation, pump failure		Normal	
3	M	69	Sinus rhythm	Complete AV block	36 hours	Heart block			
4	M	68	First degree AV block	Prolongation of PR interval	36 hours	Cerebral infarc tion			" + atrophy His bundle
5	F	51	Clinical data not available			Cardiac tam ponade			Hemorrhage transitional zone
6	M	59							"
7	F	[illegible]0	Atrial fibril lation	Atrial fibrillation	4 hours		Normal	Normal	Normal
8	M	61	Sinus rhythm	Sinus rhythm	1 day	Operation pump failure	Hematoma me-dial wall right atrium	"	
9	F	74	Sinus rhythm	Multifocal atrial rhythm	3 days	Cardiac tam ponade	Normal		
10	F	53	Sinus rhythm	Sinus rhythm	1 day		Hematoma me dial wall right atrium		
11	M	39	Clinical data not available				Normal		

currently believed to interrupt the compact AV node and His bundle

The foregoing anatomo pathologic data seem to have an important bearing on the clinical features of dissecting aneurysm of the ascending aorta Disturbances in atrioventricular conduc tion seem to correlate with the pathologic find ings of hemorrhage involving the atrioventricular nodal approaches (transitional zone of the atrio ventricular node) but sparing the bulk of the atrioventricular node and His bundle

One may wonder therefore whether the synco pal attacks that may be observed during acute episode of dissecting aneurysm are due to cerebral ischemia as generally thought or to Adam Stokes attacks instead This is of direct clinical significance since it is accepted that a rapid transition from sinus rhythm to complete heart block may lead to a delay in the automaticity of a take over at a lower junctional rhythm The fact moreover that a large part of the atrioven tricular junctional tissues is not involved by the hematoma may explain why in some instances normal conduction may be restored

The present observations support the view that constant electrocardiographic monitoring in pa tients with dissecting aneurysm is mandatory and that intravenous administration of atropine is indicated as soon as signs of atrioventricular dissociation appear

Summary

In dissecting aneurysm of the ascending aorta the hemorrhage may spread into the interatrial septum and into the area of the specialized atrioventricular junctional tissue A clinicopatho logic investigation has been performed in 48 cases with classical complete dissecting aneurysm in order to evaluate whether such hemorrhage may lead to conduction disturbances Among 42 cases with aortic dissection originating in the ascending aorta eight hearts (19 per cent) presented with hemorrhagic infiltration of the atrial septum extended to the coronary sinus Histologic exam

ination of the atrioventricular conduction tissues was performed in six of these hearts and in five without such gross evidence ("controls") In the former the hemorrhage had spread between the transitional cell zone of the atrioventricular junctional area but never actually penetrated the compact node In none of the "controls" was there any histological evidence for hemorrhage The correlation between the histologic data and the available electrocardiographic findings disclosed that atrioventricular conduction disturbances including atrioventricular dissociation were present only in cases with hemorrhage of the atrial septum It is suggested that (a) hematoma of the interatrial septum is not at all infrequent in cases with dissection of the ascending aorta (b) this complication leads to atrioventricular conduction disturbances (c) the hemorrhage preserves a large part of the atrioventricular junctional tissues thus explaining the occurrence of the atrioventricular dissociation with junctional rhythm and eventual restoration of the normal conduction

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A comparison of the size of the arterial vascular bed to the right ventricular mass in patients with chronic obstructive pulmonary disease

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It remains unclear as to whether there is a proportional increase of the coronary artery vascular bed with myocardial hypertrophy Although many studies have been reported previously these have dealt with pathological states involving hypertrophy of the left ventricle [3] or the whole heart [1] not focusing primarily on right ventricular hypertrophy In addition no studies to our knowledge have used methods giving specific ventricular weights The lack of a systematic study in this area has been noted by Baroldi and Schomazzone [5]

Our study employing postmortem coronary angiograms and a method for determining specific myocardial mass examines the relationship between the size of the coronary vascular bed and the right ventricular mass in patients dying with severe chronic obstructive pulmonary disease

Methods and materials

During a six year period 72 heart specimens were obtained on male patients known to have severe chronic obstructive pulmonary disease This represented 3 3 per cent of all autopsies performed during this period Hospital records were reviewed and those patients satisfying the following criteria for chronic obstructive pulmonary disease were selected (1) a history of chronic obstructive pulmonary disease as a major factor in the patient s illness (2) physical findings supporting the diagnosis (3) spirometric findings when available compatible with severe chronic obstructive pulmonary disease (4) gross and pathological confirmation of chronic obstructive pulmonary disease including inflated lung specimens when possible and (5) significant blood gas abnormalities compatible with chronic obstructive pulmonary disease at some time in the clinical course an arterial PO_2 (PaO_2) below 60 mm Hg and an arterial PCO_2 above 45 mm Hg was observed

During this six year period hearts were also obtained from 34 male patients known to (1) be free of cardiopulmonary disease (2) have normal postmortem angiography or showing less than 25 per cent occlusive (a value generally considered insignificant) coronary artery lesions (3) have a normal chest film and (4) have a normal body weight or exceeding 90 per cent of the lower limit of normal of a specific height* (to avoid patients with emaciation and accompanying heart atrophy) These patients then represented a control group without heart or lung disease for comparison purposes

The freshly excised hearts were obtained at autopsy and were taken to the laboratory where cannulae were placed in the left and right coro

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ination of the atrioventricular conduction tissues was performed in six of these hearts and in five without such gross evidence (controls) In the former the hemorrhage had spread between the transitional cell zone of the atrioventricular junctional area but never actually penetrated the compact node In none of the controls was there any histological evidence for hemorrhage The correlation between the histologic data and the available electrocardiographic findings disclosed that atrioventricular conduction disturbances including atrioventricular dissociation were present only in cases with hemorrhage of the atrial septum It is suggested that (a) hematoma of the interatrial septum is not at all infrequent in cases with dissection of the ascending aorta (b) this complication leads to atrioventricular conduction disturbances (c) the hemorrhage preserves a large part of the atrioventricular junctional tissues thus explaining the occurrence of the atrioventricular dissociation with junctional rhythm and eventual restoration of the normal conduction

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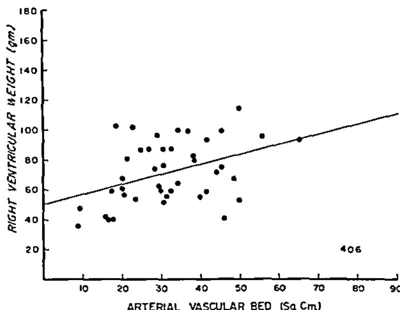


Fig 2 This graph illustrates the size of the vascular bed as measured by total planimetered area in square centimeters in all arteries greater than 1 millimeter in diameter compared to the right ventricular weight in grams in 42 patients with chronic obstructive pulmonary disease

sectional area of the coronary lumen and 5+ 76 to 100 per cent narrowing of the cross sectional area of the coronary lumen

Chronic hypoxemia was considered present if an arterial PaO below 65 mm Hg was noted for three months or longer before death in patients with stable disease Spirometry was performed during a stable state in the chronic obstructive pulmonary disease Peak abnormalities for blood gases were recorded during times of respiratory decompensation

Thirty patients of the original 72 patients with chronic obstructive pulmonary disease were excluded Of these 30 excluded patients 20 had significant atherosclerosis of the right or left coronary artery (greater than 75 per cent occlusion—a value generally agreed upon as significant in reducing coronary flow—of one or more major coronary arteries) nine had inadequate filling of the arterial tree and one had a predominant left coronary artery pattern Seven of the original 34 control patients were excluded Of these seven excluded patients six had inadequate filling of the arterial tree and one had a predominant left coronary artery pattern In all 42 remaining patients with chronic obstructive pulmonary disease and in the 27 remaining controls a distinct separation of the right and left ventricles of the postmortem x rays was possible The information in this report is limited to these patients

Results

The relationship between the right ventricular mass to the square surface area of the arterial tree in the 42 patients with chronic obstructive pulmonary disease is shown in Fig 2 In Fig 3 the relationship of the right ventricular mass to the sum of the cross sectional area of the first order arterial branches originating from the right coronary artery in this group is shown Measurements of cross sectional areas were possible in 33 of the 42 patients the overlapping of proximal arterial segments prevented complete data on the remaining nine patients Figs 2 and 3 show a definite but low correlation and are compatible with a concomitant increase of the arterial vascular bed with the development of right ventricular hypertrophy This finding is convincing when compared with Fig 4 (patients without heart or lung disease)

Right ventricular hypertrophy only was present in 24 of the 42 patients and ranged from minimal to marked in degree Left ventricular or combined hypertrophy was present in 10 patients Eight patients with pulmonary disease had normal sized ventricles The results were comparable in these groups

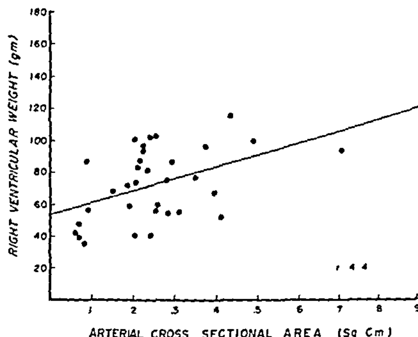


Fig 3 This graph illustrates the size of the vascular bed as measured by the sum of the cross-sectional area of all first order arterial branches originating from the main right coronary artery compared to the right ventricular weight in grams in 33 patients with chronic obstructive pulmonary disease

Chronic hypoxemia was observed in 19 patients with chronic obstructive pulmonary disease Patients with chronic hypoxemia developed a vascular bed comparable to that of the disease group as a whole

Thirty five of the 42 patients (83 per cent) had either spirometry or an inflated formalin fixed lung specimen The average spirometric test (22 of 42 patients) gave the following mean value forced expiratory volume in one second divided by the forced expiratory volume was 39 per cent ± 10 6 SD and the maximum mid expiratory flow rate was 0 42 liters ± 0 21 SD Peak abnormal blood gas values for the 42 patients with chronic obstructive pulmonary disease showed a mean arterial value for PaO of 36 ± 7 SD and a mean arterial value for PCO of 81 ± 28 SD

Although the vascular supply of the right ventricle was predominantly from the right coronary artery in 89 per cent of right ventricles from patients with chronic obstructive pulmonary disease as well as the control hearts there was an arterial supply from the left coronary system This is consistent with previous reports[3] In 38 per cent of the controls and in 39 per cent of those with lung disease the portion of the arterial vascular bed originating from the left coronary artery exceeded one millimeter in diameter This vascular bed from the left coronary artery constituted an average of 11 per cent (range 1 to 70 per cent) of the total vascular bed measured (planimetry) of both groups of patients

The average age of those patients studied was 64 years compared to 50 years of age for the controls

Discussion

The data show a definite relationship between vascular bed enlargement as determined from postmortem angiograms in those arteries greater than one millimeter in diameter and right ventricular hypertrophy occurring in patients with chronic obstructive pulmonary disease There is a marked degree of variation from one specimen to another This variation has been noted in studies comparing left ventricular mass and vascular bed size Any adverse effect of obstructive coronary disease on the development of the vascular bed has been excluded by our selection of cases Prior studies relating left ventricular hypertrophy to vascular bed size have not systematically excluded coronary obstructive disease and this has been a confusing issue in the results

Chronic hypoxemia favors the development of right ventricular hypertrophy[1] and therefore is of special interest in its effect on the vascular bed. Nineteen of the 42 patients with chronic obstructive pulmonary disease had chronic hypoxemia

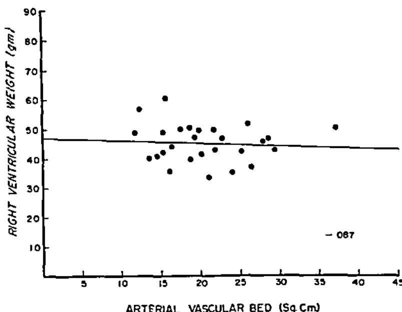


Fig 4 This graph illustrates the size of the vascular bed as measured by total planimetered area in square centimeters in all arteries greater than 1 millimeter in diameter compared to the right ventricular weight in grams in ?7 control patients without evidence of heart or lung disease

for at least three months duration but there was no difference in the degree of vascular bed enlargement with hypertrophy in these patients and that of the group as a whole

Several methods have been used to evaluate blood vessel development and size compared to enlarging muscle mass Physiological studies of blood flow estimation of vascular volume microscopic evaluation of capillary size and determination of arterial size by direct or indirect measurement [6] have been performed Despite these studies there is no uniformity of agreement concerning the consistency with which the vascular bed enlarges compared to the myocardial mass Our data have the major advantage of achieving specific myocardial mass and applying two methods of evaluating vascular volume the results of which complement each other

The relationship of the vascular bed enlargement to hypertrophy may be different in the immature animal where studies suggest there is a more fully compensatory increase of the vascular bed than we observed Right ventricular hypertrophy in chronic obstructive pulmonary disease represents acquired myocardial mass in the middle to older age patient This suboptimal vascular bed development is consistent with other reports There are few reported studies in aged animals and they indicate a poor correlation of vascular bed with ventricular mass [25] Our results confirm this and show high variability in the vascular bed development Obstructive coronary disease and hypoxemia were excluded as contributing factors in this variation

Summary

Hearts from patients dying with severe chronic obstructive pulmonary disease were examined for right ventricular mass and coronary arterial vascular bed size Normal hearts obtained from patients dying of other causes were also examined for comparison The relationship between the size of the vascular bed and ventricular mass was examined and a definite but low correlation was found Severe obstructive coronary artery disease was excluded and chronic hypoxemia did not alter the results The arterial vascular bed supplying the right ventricle of male patients with severe chronic obstructive pulmonary disease appears to undergo a compensatory increase in size as the ventricular mass enlarges but this is highly variable and incomplete

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Arrhythmia surveillance by transtelephonic monitoring: Comparison with Holter monitoring in symptomatic ambulatory patients

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Dynamic electrocardiography by means of the Holter monitor has proven its practicality and versatility as a non-invasive diagnostic tool in the evaluation of the patient with symptoms suggestive of cardiac arrhythmia.[1-3] Occurrence of such symptoms may, however, not coincide with the period of Holter recording and multiple recording periods may be required to document the cardiac rhythm at the time of symptoms. We have therefore evaluated a patient-actuated transtelephonic cardiac monitoring system (TTM) in order to determine whether it can more fully document the cardiac rhythm in symptomatic ambulatory patients. Our results are compared with simultaneous 24 hour Holter monitoring (HM).

Methods

TTM was implemented using a small, portable, battery-powered transmitter which monitors a Lead I ECG signal via two axillary electrodes.† The signal is converted to an acoustical tone which is transmitted via any telephone to the hospital monitoring station where it is reconverted into ECG form and recorded on paper and magnetic tape. The frequency response of the system is between 0.18 and 30 Hz.

Continuous 24 hour dynamic electrocardiography was carried out by means of a standard Holter monitor recording system.* The TTM and HM recordings were reviewed initially by a monitoring technician and were subsequently interpreted by one of the authors (R. G.).

Subjects and protocol. All symptomatic patients routinely referred for Holter monitoring were considered for this study. Requirements for inclusion were: (1) willingness to participate and (2) comprehension of the transtelephonic technique. Excluded from final analysis were those patients submitting an inadequate number of TTM recordings (i.e., less than one per day).

Patients were simultaneously given the transtelephonic and Holter monitors along with instruction in their use. The TTM was recorded over a seven day period. Patients were instructed to call the monitoring station with *each* occurrence of symptoms and to call routinely if they were asymptomatic for *any* eight hour period. Each period of transmission included: (1) 30 seconds of patient identification data and report of symptoms (if any), (2) 60 seconds of ECG recordings. The HM was recorded during the first 24 hours of the TTM recording period. Symptoms were recorded chronologically in a diary. Results were analyzed using a one-tailed chi squared method.

Symptoms and arrhythmias. Significant symp-

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Table I Patients reporting symptoms during the 24 hour Holter and 7-day transtelephonic monitoring period

Symptoms	Patients	Period of symptomatology		
		HM alone	*TTM alone*	*Both HM & TTM*
Total	26	2	7	17
Palpitations	15	4	4	7
Chest discomfort	15	1	7	7
Lightheadedness	10	1	6	3

Abbreviations HM = Holter monitoring TTM = transtelephonic monitoring

Several patients reported more than one symptom

toms were defined as those *potentially* attributable to or associated with an arrhythmia and included (1) palpitations (2) chest discomfort (3) lightheadedness or its equivalent Significant arrhythmias were defined as those potentially associated with symptoms and the following criteria were established tachyarrhythmias ≥ 110 beats/minute bradyarrhythmias ≤ 50 beats/minute ventricular premature contractions (VPC) ≥ 1/minute with palpitations ≥ 6/minute with other symptoms or if asymptomatic

Results

Fifty nine patients formed the initial study group Excluded from final analysis were 15 patients who failed to transmit a minimum of one transtelephonic recording per day two patients in whom technical difficulty was encountered with the HM (i e 1 patient artifact 1 patient recorder malfunctioned) two patients in whom technical difficulty was encountered with the TTM (artifact) The 40 remaining patients were included in the final analysis This group consisted of 18 males and 22 females with a mean age of 50.3 ± 2 4 (SEM) years (range 14 to 80 years) An average of 15 6 ± 0 9 (SEM) transtelephonic recordings per patient (range 7 to 36 recordings/patient) were received over the seven day monitoring period

Symptoms Twenty six of the 40 historically symptomatic patients monitored concurrently by HM and TTM had significant symptoms during the recording period (Table I) Fifteen patients reported palpitations 15 reported chest discomfort and 10 reported lightheadedness Several patients reported more than one symptom Of these 26 patients seven reported symptoms only during TTM and 17 during both HM and TTM recording periods Two patients who reported symptoms only during HM neglected to call the TTM monitoring station during these symptoms

Table II Relationship of symptoms to arrhythmias in symptomatic patients

Symptoms	Patients	No with arrhythmia	No without arrhythmia
Total	26	11	15
Palpitations	15	8	7
Chest discomfort	15	5	10
Lightheadedness	10	1	9

Several patients reported more than one symptom

Considering individual symptoms separately palpitations were reported equally with each monitoring technique (HM 11 patients TTM 11 patients) Chest discomfort and lightheadedness were reported more frequently during TTM (14 patients and nine patients) than during HM (eight patients and four patients) although these differences do not reach statistical significance

Arrhythmias Fifteen of 40 patients monitored concurrently by HM and TTM demonstrated significant arrhythmias at some time during the recording period Eleven patients demonstrated arrhythmias during symptomatic periods while six showed arrhythmias during asymptomatic periods Several patients had both symptomatic and asymptomatic arrhythmias

In these 15 arrhythmic patients the arrhythmia was documented by HM alone in three by TTM alone in three and by both HM and TTM in the remaining nine patients Both techniques were therefore equal in their ability to detect arrhythmias with each documenting the arrhythmia in 12 patients

Symptomatic arrhythmias Eleven of the 26 symptomatic patients demonstrated significant arrhythmias during symptomatic periods The remaining 15 symptomatic patients showed no such arrhythmias (Table II) Palpitations and chest discomfort were associated with significant arrhythmias in eight of 15 and in five of 15 symptomatic patients respectively while lightheadedness was usually associated with no arrhythmia (nine of 10 patients) One patient

Table III Arrhythmias in patients reporting symptoms

Arrhythmias	*Patients*	*Symptoms*			*Documentation*		
		P	*CD*	*L*	*HM alone*	*TTM alone*	*Both*
Total	11	8	5	1	1	4	6
Tachyarrhythmias	7†	5	2	0	1	5	1
Bradyarrhythmias	1‡	0	1	0	0	1	0
Ventricular extrasystoles	5	3	3	1	0	0	5

Abbreviations P = palpitations CD = chest discomfort L = lightheadedness others as in Table I
Some patients had more than one arrhythmia.
†Sinus tachycardia 5 supraventricular tachycardia 1 paroxysmal atrial fibrillation 1
‡Sinus bradycardia 1

reporting lightheadedness was found to have frequent VPCs Specific arrhythmias in these 11 patients included tachyarrhythmias in seven bradyarrhythmias in one and VPCs in five patients (Table III) Several patients had more than one arrhythmia These 11 symptomatic arrhythmias were documented by HM alone in one patient by TTM alone in four and by both devices in the remaining six patients

Of the specific arrhythmias the tachyarrhythmias were more frequently documented by TTM (six of seven patients) than by HM (two of seven patients) and were usually associated with palpitations (five of seven patients) and occasionally with chest discomfort (two of seven patients) Ventricular premature contractions were always detected by both monitoring devices and were associated with all three major symptoms

Asymptomatic arrhythmias A total of six patients had significant arrhythmias during asymptomatic periods Three of these patients were totally asymptomatic during the entire recording period These arrhythmias included VPCs in four patients severe sinus bradycardia in one and paroxysmal atrial fibrillation with a rapid ventricular response in one patient These arrhythmias were documented by HM alone in one patient by TTM alone in no patients and by both HM and TTM in the remaining five patients

Diagnostic usefulness in symptomatic patients The absence of arrhythmia during symptoms was considered to be useful diagnostic information in excluding arrhythmia as a cause for such symptoms Of the 15 symptomatic patients without arrhythmia the HM alone was useful in excluding arrhythmia as a cause for symptoms in two patients the TTM alone in six patients and both HM and TTM in the remaining seven patients

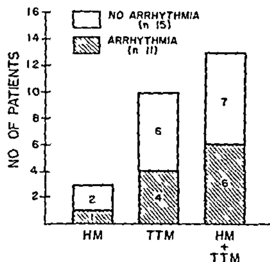


Fig 1 *The ordinate* marks the number of patients in whom either or both monitoring devices were considered useful. *The abscissa* denotes which monitoring device best evaluated the patient s symptomatology TTM is statistically more useful than HM in evaluating the significance of symptoms in symptomatic ambulatory patients (χ = 3 69 p < 0 05) Abbreviations HM = Holter monitor TTM = transtelephonic monitor

The cumulative diagnostic usefulness (Fig 1) in evaluating the significance of symptoms potentially attributable to arrhythmias is summarized as follows HM alone useful in three patients TTM alone in 10 patients and both HM and TTM together useful in 13 of a total of 26 symptomatic patients TTM was significantly more useful in this regard than was HM (χ = 3 69, p < 0 05)

EXAMPLE Patient L M is an 80 year old female who complained of intermittent palpitations (Fig 2) HM revealed an asymptomatic sinus bradycardia and a rare VPC TTM demonstrated a similar asymptomatic sinus bradycardia but also revealed a paroxysm of atrial fibril

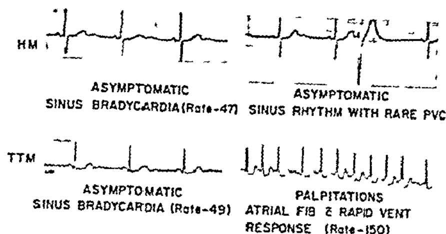


Fig 2 Example TTM confirms asymptomatic sinus bradycardia as seen with HM as well as demonstrating a paroxysm of atrial fibrillation with a rapid ventricular response during palpitations (see text) Abbreviations HM = Holter monitor; TTM = transtelephonic monitor

lation with a rapid ventricular response at which time the patient reported palpitations In this case both techniques documented a potentially important asymptomatic arrhythmia In addition TTM detected a clinically important symptomatic arrhythmia as well

Discussion

In recent years there has been a heightened awareness of the role of cardiac arrhythmias in the morbidity and mortality of symptomatic patients Since symptoms potentially attributable to arrhythmias may be infrequent or transient documentation may be difficult

Holter monitoring has been extensively used to detect such infrequent or transient arrhythmias Recommendations concerning the optimal length of Holter recording have varied Ruberman and associates have collected data which correlate the frequency and character of VPCs obtained over an hour s period of recording time with long term prognosis Lown and Wolf however have shown that while 70% of VPCs occur during the first hour of recording only 25% of high grade VPCs are seen in this period of time and only 50% during the first six hours Lopes and colleagues have suggested that a 24 hour tape increases the diagnostic yield by 16% over that of a 12 hour tape Kennedy and co workers have compared the effectiveness of several durations of continuous ambulatory Holter monitoring in patients with coronary heart disease Examination of either the initial hour of study or an hour of dynamic activity often failed to demonstrate the maximum ventricular ectopy particularly with regard to frequent or complex types Six and 12 hour recordings revealed a greater proportion of high grade ventricular ectopy but still less so than a full 24 hour recording The diagnostic yield was further significantly improved by extending the recording to 36 and 48 hours Most investigators would now recommend at least a 24 hour recording period to enhance arrhythmia detection Even this however may not be enough Morganroth and associates analyzed the spontaneous variability in the frequency of VPCs in 15 clinically stable patients with various cardiac disorders subject to 72 hour Holter recordings It was found that the hour to hour eight hour to-eight hour and day to-day variation in arrhythmia frequency was 48 29 and 23% respectively Moreover the variability between repeated three day monitoring periods was 3?%

The difficulty in documenting infrequent arrhythmias by the Holter technique is even more apparent Such arrhythmias when associated with symptoms should be more easily documented with a patient actuated monitoring system This study sought to compare a patient actuated transtelephonic monitoring system to Holter monitoring in its ability to adequately document arrhythmias in symptomatic ambulatory patients Despite such demonstrated differences in the length of Holter monitoring for optimal arrhythmia detection we elected to compare the 24 hour Holter recording the technique most often utilized for clinical arrhythmia detection with TTM Several observations were made (1) TTM was found to be statistically superior to HM in establishing the significance of

symptoms potentially attributable to arrhythmia; (2) one week of TTM appears similar to a continuous 24 HM recording in its ability to detect asymptomatic arrhythmias; (3) both techniques identified similar types of arrhythmias; (4) the majority of all arrhythmias were detected by both monitoring techniques despite the fact that TTM was recorded for only 60 seconds at a time; (6) during the one week recording period, only 26 of 40 historically symptomatic patients reported any symptoms. This would suggest the need to extend the TTM period to greater lengths in patients who have not reported any symptoms during the first week.

Several further observations were made regarding individual symptoms and arrhythmias. Palpitations, a predominant complaint reported equally during both recording periods, was associated with an arrhythmia in about half of cases and its significance was successfully evaluated equally by both techniques. Lightheadedness, on the other hand, was reported more frequently during TTM and was rarely associated with an arrhythmia; its significance was best evaluated by TTM. Chest discomfort, the co-dominant complaint, was frequently reported during both periods of monitoring and was sometimes associated with an arrhythmia; its significance was evaluated correctly more often by TTM.

Hasin and colleagues[10] have evaluated TTM in 200 patients for up to 31 days. These patients were suspected of having transient arrhythmias or ischemic events or were being monitored on antiarrhythmic drug therapy. TTM documented arrhythmias in 88% of cases of those with suspected arrhythmias. Supraventricular arrhythmias were found most often (65% of cases) while VPCs were also frequent (40% of cases). Nineteen % of arrhythmias were detected during asymptomatic routine call-in periods. These results are similar to our observations.

Our results indicate that TTM both complements and supplements HM in symptomatic patients; it should be of particular value in the patient with infrequent symptoms. TTM has several advantages over HM, both practical and theoretical. It allows for patient monitoring over an extended period of time until symptoms occur without the need for repeated costly Holter recordings, and it provides prospective on-line patient monitoring with the potential for immediate patient access to the health care delivery system. Potential disadvantages include failure to capture very transient arrhythmias or those rendering the patient incapable of contacting the monitoring system. It is apparent that TTM emerges as a simple, accurate, and useful tool for arrhythmia surveillance in symptomatic patients.

Summary

We have evaluated a patient-actuated transtelephonic monitoring system (TTM) in order to determine its ability to document the cardiac rhythm at the time of symptoms; results have been compared to a simultaneously recorded 24 hour Holter Monitor (HM).

Forty patients submitted an average of 15.6 TTM recordings/patient over a 7 day recording period. Twenty-six patients reported significant symptoms during the period of study; 11 had demonstrated arrhythmias and these were documented by HM alone in one, by TTM alone in four, and by both HM and TTM in six.

In 15 patients no arrhythmia was seen during symptoms. HM alone was useful in excluding arrhythmia as a cause for the symptoms in two patients, TTM alone in six patients, and both in the remaining seven patients. Cumulative diagnostic usefulness in evaluating the significance of symptoms potentially attributable to arrhythmia is summarized: HM alone useful in three patients, TTM alone useful in 10 patients, and both HM and TTM useful in 13. TTM was significantly more useful than HM ($\chi^2 = 3.69$, $P < 0.05$).

Of note is that six patients had significant arrhythmias during asymptomatic periods, including VPCs (four), severe sinus bradycardia (one), and rapid atrial fibrillation (one). In these few patients both techniques appeared equally able to document asymptomatic arrhythmias.

These observations demonstrate that TTM carried out over a 7 day period is superior to a 24 hour Holter monitor recording in its ability to establish the significance of symptoms potentially attributable to arrhythmia and appeared equally sensitive to HM in demonstrating periods of asymptomatic arrhythmia.

TTM can therefore be considered a simple, accurate, and useful technique for arrhythmia surveillance in the symptomatic patient.

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Experimental and laboratory reports

Analysis of human atrial fibrillatory waves using monophasic action potential technique

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Atrial fibrillation is a rather common arrhythmia and it has been known as an ECG diagnosis since 1909[1] The conversion of atrial fibrillation into sinus rhythm is of value to prevent atrial embolization and thrombosis and to improve the hemodynamic effectiveness of the heart[2, 3]

The difficulties are still related in the maintenance of sinus rhythm after successful conversion of atrial fibrillation

The amplitude of the fibrillatory waves was correlated to the etiology of atrial fibrillation and to the size of the left atrium in order to analyze the possible efficacy of conversion to sinus rhythm and the sinus rhythm stability[5]

Atrial fibrillation can be better analyzed using monophasic action potentials recordings (MAP) which allow an overamplification of the electrical atrial activity[6]

The purpose of the present paper is to analyze the fibrillatory waves through MAP recordings in patients with atrial fibrillation of different etiology

Patients and method

Twenty nine patients five women and 24 men with atrial fibrillation were investigated after informed consent had been obtained

These 29 patients were divided in four groups

A Eight patients with rheumatic heart disease and signs of heart failure

B Fourteen patients with coronary heart disease also with heart failure

C Four patients with a paroxysmal form of atrial fibrillation one with WPW syndrome an operated atrial septal defect and two with idiopathic forms

D In this last group we have put together three patients—one with operated mitral stenosis and two patients with coronary heart disease but all without cardiac failure and with heart size in the normal ranges

The patients were investigated in the fasting non sedated state and no cardioactive or antiarrhythmic drugs were given three days before the study

Monophasic action potentials were recorded in each patient using a suction electrode catheter technique The bipolar electrode catheters were introduced percutaneously into the right atrium without x ray control as a bedside procedure[3, 7, 8]

Only continuous strips of stable tracing were included in the study the duration and the amplitude being measured for each complex The duration was measured at the base of each complex and for the amplitude we have used a baseline coincident with the lowest part of the tracing the same for all waves Between 100 and 200 waves were measured from each recording

For statistical analysis the following data concerning the duration of MAP of fibrillatory waves were calculated the average duration the standard deviations and the standard errors and then the data were compared by χ test and by analysis of variance In the same way the frequency distribution of the duration of MAP fibrillatory waves was analyzed and compared

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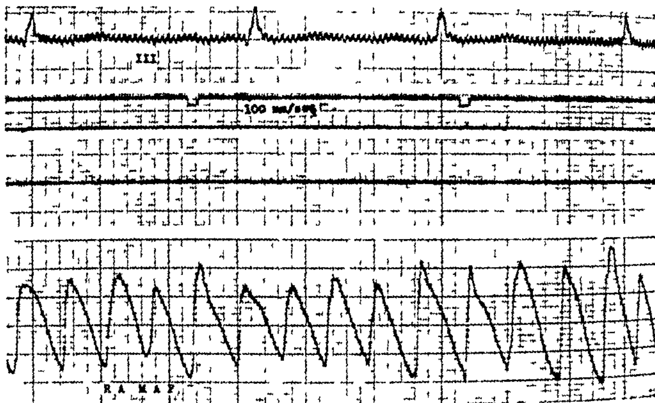


Fig 1 Simultaneous recordings of Lead III and right atrial monophasic action potential (RA MAP) in one patient with coronary heart disease Paper speed 100 mm /sec

Table I The frequency of the fibrillatory waves/minute

Group	A	B	C	D	F	Total
Minimum	34?	312	430	438	4?0	312
Maximum	534	660	570	510	570	660
$\bar{X}$	449 [illegible]	458	[illegible]10	4 [illegible]	493 71	464
S	60 4	101 7	63 69	36 16	[illegible]3 63	81 47
S	21 35	2[illegible] 18	31 84	20 88	?0 27	15 13

Table II Fibrillatory wave MAP duration in msec

Group	A	B	C	D	E	Total
Minimum	112 70	94 90	109 70	116 70	109 70	94 90
Maximum	174 [illegible]0	183 [illegible]0	1[illegible]0 10	128 80	130 10	183.50
$\bar{X}$	1[illegible] 16	[illegible]1	118 55	123 03	1?0 47	131 01
S	10 69	[illegible]	8 48	6 06	[illegible] 3[illegible]	20 92
S	6 60	[illegible]	4 24	3 50	2.77	3 88

Table III The number and distribution of MAP duration in fibrillatory waves

Duration in msec	A	B	C	D	Total
40		10			
50		27			
60		26	1		
70	11	49	3		
80	20	40	11	3	
90	[illegible]6	83	37	15	
100	11[illegible]	19?	93	60	
110	87	171	84	54	
120	1[illegible]6	?40	105	108	
130	148	253	83	71	
140	191	?94	57	71	
150	170	246	14	46	
160	90	151	3	13	
170	54	131			
180	36	9[illegible]			
190	19	61			
200	11	28			
210	7	13			
220	3	14			
230		5			
240		2			
	1151	2132	491	442	4216

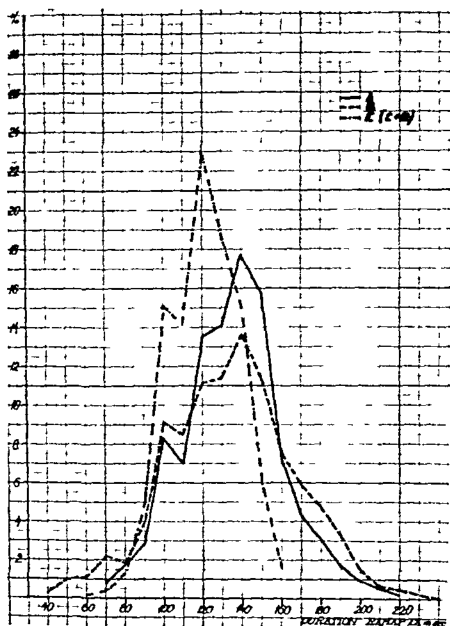


Fig 2 The relative frequency distribution of the monophasic action potential duration in groups A B and E

The correlation between duration and amplitude of MAP waves was done also

The patients were followed up for more than one year and it is worth remarking that all the patients from groups C and D were successfully defibrillated and they are still in stable sinus rhythm after one year while only eight were successfully defibrillated from groups A and B and all relapsed to atrial fibrillation in this period and in five we did not succeed in converting the arrhythmia

Results

The atrial activity recorded at different sites in the right atrium showed the same rate and had a similar configuration

Not much attention was paid to the amplitude of the MAP the studies being focused on the duration

In all four studied groups there was a significant correlation between the amplitude and the duration of the fibrillatory MAP waves

The similitude in clinical and evolution aspects

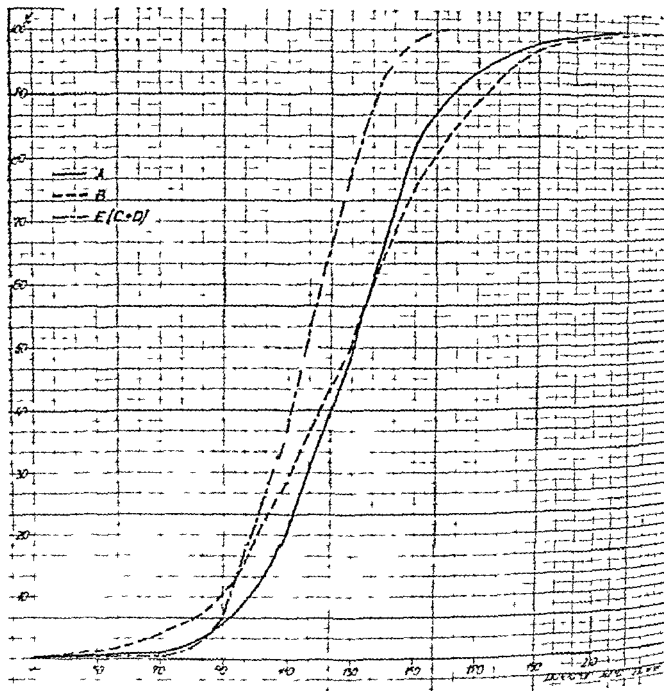


Fig 3 r] ł ŋ r pha a ıcn potential duratı n ın groups A B and E

ın ‹ ‹ s th ı ılar tatı tı al data allowed ıs ze ar ap ‹ and D tı gether whi h re a ler l› a rew la ıfication group F ſr ı ıı data erning the rate of fibrillat ‹ ‹ j erte ł ın Ta le I and those ‹ n ‹ ‹ MAI are given ın Table II

The freque ı rFu ı ſ MAI luratı n for all group r e‹ ‹ n Table III

In order ı ınpare the data presented ın Table III the relative frequency distribution of the MAP duration was constructed as shown ın Fig 2 Groups C and D having a similar relative frequency distribution were drawn together as group E

It ıs obvious from this figure that ın groups A and B there are three peaks at 100 120 and 140 msec In groups C and D (E) there are only two peaks at 100 and 120 msec

The highest frequency appeared ın groups A

Table IV The quantitative relations of populations at peaks of 100 120 and 140 msec

Group	*Duration*		
	100 msec	*120 msec*	*140 msec*
A	20 5%	28%	51 5%
B	28 00%	20 00%	50 00%
E(C + D)	36%	64%	

and B at 140 msec while in group E it appeared at 120 msec and without peak at 140 msec

The relations between the surfaces occupied by the subpopulations of waves which form the peaks at 100 120 and 140 msec are presented in Table IV

In Fig 3 the distribution functions of the MAP duration are drawn In groups C and D the waves with short duration are more frequent and they are narrowly grouped In groups A and B there are waves with a longer MAP duration and with a higher degree of dispersion

To compare many groups simultaneously for a quantitative analyse we have used the statistical method analysis of variance The results are shown in Table V

Significant statistical differences were found at 120 msec using the combination of groups A B C D or A B C + D and no significant differences were found at 100 and 140 msec

The absolute number of waves with 100 120 and 140 msec duration was compared using the χ^2 test The results are shown in Table VI

From this table it is possible to demonstrate that using the absolute values we obtain the same results as in the case of the analysis of variance at 120 msec and also that there are significant differences between the groups A/C B/C B/D A/C + D B/C + D at 100 msec

Table V Average values standard deviations and standard errors of MAP duration in groups of 100 120 and 140 msec compared by analysis of variance

Groups	*100 msec*	*120 msec*	*140 msec*
A	11 05	15 43	17 75
	7.27	6.26	9 86
	6	7	8
B	12.83	11 96	13 57
	8.38	7.54	8 44
	10	13	14
C	15 36	20 92	14 96
	11 32	7 90	11.22
	4	4	4
D	14 64	25 47	15 01
	7 44	4 46	4 62
	3	3	3
A B E (C + D)	0 05>p (0.37707)	0 05>p>0 01 ——— (5 51207)	0 05>p (0 56973)
A B C D	0 05>p (0.24999)	0 05>p>0 01 ——— (3.86829)	0 05>p (0 365 6)

Discussion

Course and fine fibrillatory waves are a well known electrocardiographic aspect and their size has been explained by atrial dimensions or wall thickness etiology of the heart disease the extent of atrial damage and other factors

MAP recordings during atrial fibrillation allow a better analysis of the fibrillatory waves which can be grouped according to the duration or amplitude The slow intermediate or high rate of the fibrillatory waves, together with the absolute or relative per cent distribution of the duration of MAP are probably dependent on the electrophysiologic properties of the atrial muscle [6 11]

In the present study special attention was given to the MAP duration of the fibrillatory waves the duration being a reliable index of the refractoriness of atrial myocardium and in this way this component may be of value in the estimation of the electrical conversion efficacy and the sinus rhythm stability after conversion [2 3]

From Tables I and II it is obvious that in regard to the rate and duration of MAP in atrial fibrillation between groups A and B and also between groups C and D there are no differences The differences appear only between groups A and B on one side and groups C and D (E) on the other side

Using the relative frequency distribution of the MAP duration in groups A and B we found three peaks at 100 120 and 140 msec with the highest value at 140 msec and with a similar shape of a relative frequency distribution In groups C and D (or E) there are only two peaks at 100 and 120 msec with the maximum at 120 msec (Figs 2 and 3 and Table IV)

From the distribution function of the MAP

Table VI Number of waves at a duration of 100, 120, and 140 msec compared by χ^2 test

Groups	100 msec	120 msec	140 msec	T…
A	112	156	191	1…
B	192	210	294	2…
C	93	105	57	4…
D	60	108	71	4…
E(C + D)	153	213	128	5…
χ^2				
A/B	$0.50 > p > 0.40$	$0.20 > p > 0.10$	$0.10 > p > 0.05$	
A/C	0.0005 p	$0.001 > p > 0.0005$	$0.05 > p > 0.025$	
A/D	$0.10 > p > 0.05$	0.0005 p	$0.90 > p > 0.80$	
A/C + D	0.0005 p	0.0005 p	$0.20 > p > 0.10$	
B/C	0.0005 p	0.0005 p	$0.30 > p > 0.20$	
B/D	$0.025 > p > 0.01$	0.0005 p	$0.40 > p > 0.30$	
B/C + D	0.0005 p	0.0005 p	$0.99 > p > 0.975$	
C/D	$0.10 > p > 0.05$	$0.50 > p > 0.40$	$0.20 > p > 0.10$	

duration. It is also evident that groups A and B have a longer duration and a higher dispersion of the MAP, while in groups C and D (E) the MAP is shorter and more narrowly distributed.

Using analysis of variance, significant statistical differences were found at the peak of 120 msec between groups A and B on the one hand and C and D (E) on the other ($0.05 \; p < 0.01$).

We have found significant differences between groups A and B and groups C and D using the absolute number of waves at the peaks studied by χ^2 test. The differences were significant at 120 msec, but also at 100 msec (Tables V and VI).

It appears clear from this statistical analysis that there are two different types of atrial fibrillations—the first type including groups A and B without differences between each other, and the second type including groups C and D, also very similar to each other.

Since in group A there are patients with rheumatic heart disease and in group B patients with coronary heart disease, it can be said that concerning the characteristics of the fibrillatory waves there are no differences between these two kinds of heart diseases.

In group C we have placed the paroxysmal forms of atrial fibrillation and in group D we put patients with different etiology but without heart failure and with almost normal heart size. Between these groups we have not found any differences concerning the analysis of the fibrillatory wave.

The successful conversion of atrial fibrillation with DC shock and sinus rhythm stability after conversion are in agreement with our findings. Successful defibrillation and stable sinus rhythm for more than one year was found in groups C and D as opposed to groups A and B, where only eight from 13 patients had relapsed into atrial fibrillation during the follow-up period.

Taking into account our data, which are still rather poor, we agree with the authors who found that in patients with mitral valvular disease and ischemic heart disease, there are no notable differences. In the same way we agree with the idea that solitary atrial fibrillation has a high rate of the fibrillatory wave and a shorter duration of MAP (two cases in group C in our study).

Our data are not in accordance with the s… ment that the atrial fibrillation with slower r… and longer MAP duration of the fibrillatory w… can be more easily converted to sinus rhyt… and if converted, that these patients hav… greater tendency to maintain it.

Patients in atrial fibrillation having charac… istics similar to group C and D are more prone… gain and to maintain sinus rhythm. At the sa… time the patients who were included in th… groups are in a rather good clinical state, witho… signs of heart failure and with no radiologic … heart in evidence. Perhaps the electrophysiolo… ical properties of their myocardium are very clo… to the normal and the fibrillatory wave charac… teristics obtained in these patients correspond t… an almost normal myocardial state.

We may consider that the efficacy of DC shoc… and sinus rhythm stability can be predicted using… clinical parameters only. A patient with atria…

fibrillation and very close to a normal state of myocardium has a good prognosis concerning the evolution of his arrhythmia

Summary

In 29 patients with atrial fibrillation using the monophasic action potential technique the fibrillatory waves were recorded and analyzed by statistical methods Concerning the characteristics of the fibrillatory waves there are no differences between patients with rheumatic heart disease and with coronary heart disease The patients with paroxysmal forms and those without heart failure and with normal heart size have similar statistical data with regard to their fibrillatory waves From the data presented it could be possible to predict the efficacy of conversion to sinus rhythm and also the sinus rhythm stability after conversion

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Central and peripheral receptor areas in the reflex response to acute experimental hyperosmolality

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Previous studies have demonstrated that abrupt increases in systemic plasma osmolality produced by the injection of hyperosmolar agents can induce major hemodynamic changes including marked arterial hypotension Furthermore the systemic injection of hyperosmolar solutions is capable of initiating reflex vascular responses in isolated peripheral tissue contributing perhaps to the systemic hemodynamic alterations Many possible receptor areas might be responsible for initiating the neurogenic reflex response to acute hyperosmolality

The present study attempted to investigate general receptor areas which might be activated by acute hyperosmolality resulting in reflex alterations which may affect the hemodynamic status of the organism The reflex response was studied using the isolated innervated constant flow perfused gracilis muscle preparation

Materials and methods

Twenty three mongrel dogs (weighing 17 to 38 kilograms) were anesthetized with sodium pentobarbital (25 mg /Kg) or chloralose (80 mg /Kg) with supplemental doses given as needed The responses with both anesthetic agents were similar The animals were intubated and ventilated with room air using a constant volume Harvard respirator A catheter was placed in the external jugular vein for the administration of drugs and fluids Anticoagulation was achieved with Heparin (10 000 units intravenously) with supplemental doses (2 000 units) given every two hours A brachial artery was cannulated for measurement of arterial pressure The pressures were recorded on a multi channel Sanborn (Model 769R, with P23DB transducers) or a Hewlett Packard recorder (Model 7700 with 1280-C transducers)

An isolated innervated constant flow perfused gracilis muscle preparation was used in all studies The gracilis muscle was dissected free from all surrounding tissue except for its major artery vein nerve supply and tendons. The gracilis artery was cannulated with polyethylene tubing and flow to the muscle was maintained constant by an occulsive rotary pump (Travenol) Blood was supplied to the pump perfusion system by a cannulated brachial artery The perfusion system tubing was left sufficiently long to allow a two to three minute circuit time (delay circuit) A T tube in the arterial inflow tubing allowed continuous monitoring of perfusion pressure

The isolation of the muscle preparation was tested by turning off the perfusion pump and demonstrating a fall in perfusion pressure to values associated with critical closing pressure and an absence of pressure oscillations. The presence of intact and functioning neurogenic pathways to the muscle was tested by observing reflex muscle responsiveness to other known reflexogenic stimuli such as systemic hypoten

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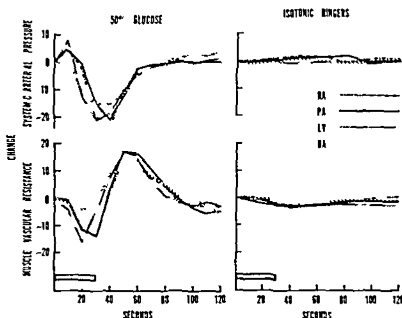


Fig 1 Changes in systemic arterial pressure (*upper panel*) and reflex alterations in muscle vascular resistance (*lower panel*) following injection of 50 ml of 50% glucose (*left panel*)and 50 mL of isotonic Ringer s lactate (*right panel*) over 30 seconds (*cross hatched bar*) The sites of injection are *RA* (right atrium) *PA* (pulmonary artery) *LV* (left ventricle) and *DA* (distal thoracic aorta) Mean response values (per cent change from control) are plotted for each 10 seconds following the onset of injection

Table I *Systemic hemodynamic and reflex muscle response to area injections of 50% glucose*

Site of injection	*SAP*		*MVR*		
	Control (mm Hg)	*Peak response (% change)*	*Control (*)*	*Vasodil (% change)*	*Vasocon (% change)*
RA	137±5	−23 2±2 8	9 4+1 0	−13 6±2.9	14 5±2.9
P value		<0 001		<0 001	<0 001
PA	13?±4	−21 1±3 0	10 0+1 1	−13 4±2.6	17 9±3 ?
P value		<0 001		<0 001	<0 001
LV	13?±5	−?0 8±3 5	9 7±1 1	−15 9±2.6	16.9±4 4
P value		<0 001		<0 001	<0 01
DA	135±5	−15 1±2 2	8 5±0 8	−4 2±1 7	11 5±3 5
P value		<0 001		<0 05	<0 01

All values represent peak response (mean ± SE) P alu represents significance of response relative to control. SAP = systemic arterial pressure MVR = muscle vascular resistan RA = right trium PA = pulmonary artery LV = left ventricle DA = distal aorta.
* = mm. Hg/ml. per 100 g pe minute

and lung hyperinflation Circulating chemical and humoral factors were excluded from contributing to alterations in muscle vascular resistance during the initial two minutes following a given intervention by means of the delay circuit incorporated into the perfusion system Thus since isolation was assured and circulating humoral factors were excluded but neurogenic pathways were intact any alteration in muscle perfusion pressure which followed a given intervention within the 2 minute circuit delay could only be reflex in origin Further since blood flow to the muscle was kept constant such alterations in muscle perfusion pressure reflect proportionate changes in muscle vascular resistance

Right atrial and pulmonary artery catheterization were performed utilizing a flow-directed catheter Left ventricular and distal thoracic aortic catheterizations were done with a pigtail catheter inserted via the femoral artery

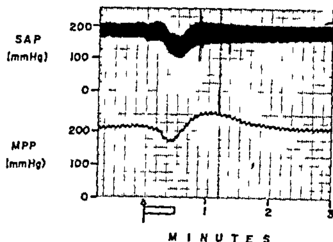


Fig 2 Response of an innervated constant flow perfused gracilis muscle preparation to left ventricular injection of 50 ml of 50% glucose *SAP* = systemic arterial pressure *MPP* = muscle perfusion pressure *Arrow* indicates start of injection *Bar* represents period of injection Time (minutes) following onset of injection is shown

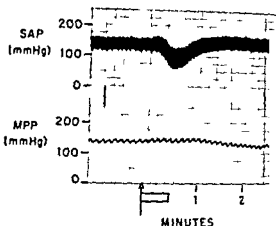


Fig 3 Response to 50% glucose injected into the left ventricle is shown following local α adrenergic blockade of gracilis muscle Despite profound alteration in systemic arterial pressure the anticipated reflex response of the muscle abolished by α adrenergic blockade Abbreviations symbols are as in *Fig 2*

In 13 animals 50 ml of 50% glucose was injected over 30 seconds into the right atrium pulmonary artery left ventricle and distal thoracic aorta in random sequence This injection results in a peak increase in plasma osmolality of approximately 100 mosm /Kg at 30 seconds[3] A 30 minute period separated each injection to allow full recovery and stabilization Systemic arterial pressure and muscle perfusion pressure were continuously monitored In seven of these dogs the response to isotonic Ringer s lactate was studied using identical techniques

The effect of systemic β adrenergic blockade (propranolol 1 5 mg /Kg intravenously) on the systemic arterial pressure and muscle reflex response to left ventricular injection of 50% glucose was studied in 10 animals In five animals the reflex muscle response following local α adrenergic blockade of the muscle (dihydroergotamine 900γ into the gracilis muscle artery) was evaluated

Results

Changes in systemic arterial pressure (SAP) Control and peak response values recorded in 13 animals are shown in Table I In all animals regardless of injection site systemic arterial hypotension resulted from 50% glucose injections The peak decrease in SAP occurred 30 to 40 seconds after the start of the injection At every injection site the maximal decrease in SAP from control values was highly significant ($p < 0.00$ The SAP response was qualitatively and quantitatively similar for the right atrium pulmonary artery, left ventricle and distal thoracic aorta injections Two minutes after the start of injection SAP returned toward control values Fig graphically displays these observations

No significant response was seen following injection of 50 ml of isotonic Ringer s solution any injection site (Fig 1)

Reflex changes in muscle vascular resistance The reflex response in the isolated gracilis muscle was recorded in 13 animals A biphasic response characterized by initial vasodilatation and followed by vasoconstriction was seen in all animals After an injection of 50% glucose was begun maximum vasodilatation occurred at 20 to 30 seconds while maximum vasoconstriction occurred 50 to 60 seconds after the start of the injection Mean changes in muscle vascular resistance from control are shown in Table I and are graphically displayed in Fig 1 The mean reflex response was qualitatively and quantitatively similar for the right atrium pulmonary artery and left ventricle injection sites The reflex vasodilatation response to hyperosmotic glucose injection in the distal thoracic aorta however was significantly ($p < 0.05$) attenuated, although its timing was similar (20 to 30 seconds) to the more central injection sites

Isotonic Ringer s lactate injected at the same

volume and rate produced no significant response in muscle vascular resistance regardless of injection site (Fig. 1).

A representative response to a 50 ml injection of 50% glucose into the left ventricle is shown in Fig. 2. Following injection in this study the SAP fell from a control value of 205/165 to 165/100 mm Hg at 34 seconds. Concomitantly muscle perfusion pressure fell from a control value of 212 to 168 mm Hg at 24 seconds. This vasodilation response was followed by an increase in perfusion pressure above control values to 225 mm Hg at 60 seconds. SAP and muscle perfusion pressure returned to control values by two minutes.

Effect of local α adrenergic blockade. Local α adrenergic block of the muscle by dihydroergotamine in five dogs abolished the reflex responses of the muscle, both vasodilatation and vasoconstriction. A representative response following α adrenergic blockade is shown in Fig. 3.

Effect of systemic β adrenergic blockade. The systemic hemodynamic and peripheral muscle reflex response to left ventricular injection of 50% glucose before and after systemic β adrenergic blockade (10 animals) is displayed in Fig. 4. After systemic β adrenergic blockade the fall in SAP following LV injection was significantly greater than that observed in the same animals before blockade (45.5 ± 5.2 versus 28.5 ± 6.2% from control, $p < 0.05$). In addition, systemic β adrenergic blockade resulted in an insignificant attenuation of the initial reflex muscle vasodilatation phase (−8.4 ± 2.4 versus −11.1 ± 2.8% from control, $p > 0.05$) but a significant accentuation of the later vasoconstriction phase (46.9 ± 9.0 versus 16.9 ± 5.9% from control, $p < 0.001$).

Discussion

These experiments were intended to expand on previous observations that systemic injection of hyperosmolar solutions initiate profound hemodynamic changes including potent reflex alterations in peripheral tissue. The study was designed to investigate the relative contribution of general receptor areas which might be activated by abrupt osmolality changes and might initiate the reflex responses. The data show that following injections of 50 ml of 50% glucose into either the right atrium, pulmonary artery, left ventricle, or distal thoracic aorta, systemic hypotension consistently occurs with each injection site. In addition, a reflex response in isolated

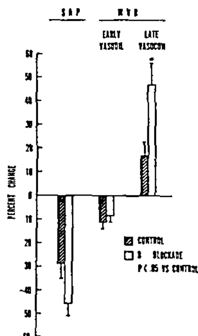


Fig. 4. Effect of systemic β adrenergic blockade with propranolol on the responses to left ventricular injection of 50% glucose. *SAP* = systemic arterial pressure. *MVR* = muscle vascular resistance. *vasodil.* = initial reflex vasodilatation. *vasocon.* = later reflex vasoconstriction. *Each bar represents* mean per cent change from control ± SE. *Asterisk* denotes statistically significant differences.

peripheral muscle was observed consisting of initial reflex vasodilatation and followed by reflex vasoconstriction. This reflex muscle response was qualitatively and quantitatively similar with right atrial, pulmonary artery, and left ventricular injections. Injection into the distal thoracic aorta, however, produced a significantly attenuated reflex vasodilatation response while late reflex vasoconstriction was similar to that observed from the other area injections.

Since the major aim of this study was to assess the reflex responses observed with different area injections, assurance had to be given that the responses observed in the muscle were reflex in origin. In each experiment tissue isolation was demonstrated and circulating humoral factors were excluded by means of the delay circuit. Thus alterations in muscle vascular resistance which occurred within two minutes following the injection of a hyperosmolar solution could only occur via nerve pathways which in each study were shown to be intact and functioning.

The injection of a hyperosmolar solution into a specific potential receptor area produces an

abrupt elevation in the plasma osmolality at that site as well as at potential receptor sites distal in the circulation to that injected site Thus injection of 50% glucose into the pulmonary artery could excite receptors in the distribution of the pulmonary artery as well as potential receptors located in the left heart and systemic arterial circulation Potential receptors proximal to the site of injection would not be in contact with hyperosmolar blood until complete circulation of blood occurs Thus differences in reflex responses observed with different area injections must be interpreted cautiously and only after thorough analysis of quantitative and qualitative differences in response as well as differences in timing of reflex responses

Analyzing the data in this manner it can be seen that injection into the right atrium pulmonary artery and left ventricle produced similar reflex responses quantitatively and qualitatively with only minimal and statistically insignificant differences in onset of response with right atrial and pulmonary artery injection (Fig 1) Thus the data indicate that important receptor sites exist at the level of or distal to the left ventricle The data however do not exclude the possibility that active receptor sites are present between the right atrium and left ventricle In this regard a previous study has shown that injection of hyperosmolar agents into an isolated lobe of the lung resulted in reflex vasoconstriction in peripheral muscle As such pulmonary receptor sites may well participate in the reflex response but alone cannot account for the complex responses observed

Reflex muscle vasodilation was significantly diminished with injection into the distal thoracic aorta when compared with the more proximal injection sites It may therefore be concluded that receptor areas between the left ventricle and distal thoracic aorta importantly influence this initial vasodilatation response Other studies have suggested that blood pressure and reflex heart rate changes may occur with injection of hyperosmolar solutions into the coronary circulation and cerebral circulation and these potential receptor areas may contribute to the reflex response to acute systemic hyperosmolality Studies utilizing injection into isolated cerebral and coronary preparations will be necessary to precisely define their roles

Although reflex vasodilatation is quantitatively less pronounced with distal thoracic aorta injection a significant response was still observed suggesting that peripheral receptor areas may b participating in the reflex response to hyperosmolality The possibility cannot be totally exclude that hyperosmolar solutions circulated and stim ulated more central receptor areas however th onset of the reflex response with distal thorac aorta injection was not delayed (Fig 1) sug es ing that peripheral receptors do in fact partic pate and adding weight to the hypothesis tha multiple receptor sites are activated by acut hyperosmolality

The late phase of the reflex response is one c vasoconstriction in peripheral muscle tissue Th exact mechanism of this reflex phase is uncerta Consideration must certainly be given to th possibility that the arterial hypotension whic develops after the injection of hyperosmolar solu tions activates baroreceptor mechanisms whic reflexly initiate peripheral vasoconstriction N data were obtained in this study to separate suc a baroreceptor mediated component from a hy perosmolality initiated reflex response howeve in a previous study using a similar preparatio eliminating baroreceptor influences by bilater cervical vagotomy and maintaining carotid sinu pressure constant did not fully abolish the vaso constriction phase of the reflex response t central venous injection of 50% glucose Thus th vasoconstriction phase observed in our studi may not be accounted for by baroreceptor mech anisms alone a reflex response to hyperosmolal ty per se is likely to be operative as well

Studies were performed with sympathet blocking agents in an attempt to investigate som of the neurogenic pathways involved The abol tion of both the reflex muscle vasodilatation an vasoconstriction phases with local muscl α adrenergic blockade alone suggests that th primary neurogenic effector mechanism underly ing the biphasic reflex responses in muscle is firs α adrenergic withdrawal causing vasodilatio followed by α adrenergic stimulation resulting i vasoconstriction With systemic β adrenergi blockade the initial reflex vasodilatation phase i the isolated muscle was not significantly altere while the later vasoconstriction phase of th reflex response was markedly accentuated It i likely that the greater degree of systemic hypo tension observed following β adrenergic blockade attributable to impaired cardiac sympathet

responsiveness enhanced baroreceptor vasoconstrictor mechanisms

Thus acute experimental hyperosmolality initiates a complex series of direct and reflex hemodynamic alterations Multiple receptor sites appear capable of initiating the reflex vascular adjustments to hyperosmolality While particular attention must be directed to the coronary and carotid circulation peripheral receptor mechanisms may be operative as well

These experimental observations may have important clinical implications with regard to the administration of hyperosmolar plasma expanders which are frequently centrally delivered as well as with regard to angiographic procedures where large amounts of hyperosmolar contrast media are injected at various sites in the circulation

Summary

Acute experimental hyperosmolality has been shown to initiate reflex vascular adjustments in peripheral tissue This study attempted to further investigate the general receptor areas which might initiate these reflexes in anesthetized dogs

Injections of 50 ml of 50% glucose were made over 30 seconds in random sequence into the right atrium pulmonary artery left ventricle and distal thoracic aorta Systemic arterial pressure fell in all animals with no significant differences observed between injection sites The vascular resistance of the isolated innervated constant flow perfused gracilis muscle preparation exhibited a biphasic reflex response characterized by initial reflex vasodilatation and followed by reflex vasoconstriction The reflex responses to right atrial pulmonary artery and left ventricular injections were quantitatively and qualitatively similar The reflex muscle vasodilation response was however significantly diminished following the injection in the descending aorta

Local α adrenergic blockade of the muscle abolished the reflex response in the muscle Systemic β adrenergic blockage resulted in accentuated hypotension and enhanced reflex muscle vasoconstriction Isotonic Ringer s solution produced no response from any injection site

The reflex response to acute experimental hyperosmolality appears to be complex with multiple receptor areas central and peripheral participating These experimental observations are clinically relevant during central administration of plasma expanders as well as various angiographic procedures

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Left atrial overload A hemodynamic, echocardiographic electrocardiographic and vectorcardiographic study

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The electrocardiogram an established non invasive technique has long been employed to detect alterations of cardiac anatomy and physiology Although the electrocardiogram displays only the temporal and spatial relation of cardiac electrical activity transmitted to the chest wall years of experience with clinical and anatomical correlations have allowed inferences to be made from the electrocardiogram about heart chamber size wall thickness and pressure or volume overload states The introduction of computer techniques permitting rapid efficient and reproducible analysis of electrocardiographic data has further increased the attractiveness of the electrocardiogram in cardiac diagnosis The inferences made regarding left atrial size and pressure from the electrocardiographic P wave inscription is one such controversial area where these inferences have been made P wave abnormalities have been thought to reflect left atrial hypertension[1,2] left atrial enlargement[3,5] altered conduction[7] or combinations of these and other factors[8,11] Indeed in the setting of acute myocardial infarction two investigators reported significant correlations of P wave morphology with left ventricular filling pressure and its serial change[1,2] yet these studies did not investigate the atrial size of their patients Studies relating the electrocardiogram to both left atrial pressure and size have shown that atrial volume is better correlated with P wave morphology than is the atrial pressure[3,11]

In order to establish the value of the P wave for estimating left atrial size and pressure and predicting changes in these parameters it would be necessary to evaluate all three of these interdependent variables not only on initial study but sequentially in patients undergoing physiologic changes. A sufficient number of studies is necessary to avoid misleading conclusions resulting from the expected variations of small sample sizes[1,4]

We therefore designed this study to obtain simultaneous and serial pulmonary artery balloon occlusion pressures echocardiograms, electrocardiograms and computer assisted vectorcardiograms in a group of patients with unstable cardiologic difficulties commonly encountered in a general hospital and have evaluated these interdependent parameters with respect to each other as changes occurred

Materials and methods

Sixty one patients admitted to the Medical Intensive Care Unit of the Veterans Administration Hospital Washington D C, clinically requiring hemodynamic monitoring constitute our population study

Patients ranged in age from 26 years to 8? years

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Table I Disease categories of study patients

	Number of patients	%
Coronary artery disease	42*	69
14 alone		
11 with hypertension		
11 with acute myocardial infarction		
6 with hypertension and acute myocardial infarction		
Hypertension	3	5
Primary myocardial disease	8	13
Other disease entities†	8	13
Total	61	100

*Diagnosis probable 14 patients, definite 28 patients; mitral regurgitation in 3 patients.
†Includes pulmonary disease, sepsis, pericardial effusion, chronic renal failure, severe anemia.

with a mean age of 56 years; all were men. Diagnostic definition of the study group is detailed in Table I. Our population was that seen in a general hospital coronary care unit with the majority of patients having coronary artery disease, hypertension, or primary myocardial disease. None of our patients had rheumatic valvular disease as defined clinically or echocardiographically. Therapy for each patient was determined by the physicians primarily managing the patient. Study observations and measurements were made amidst therapeutic modalities utilized in the care of these patients for both their cardiac and noncardiac diagnoses. Patients were studied at the time of Swan-Ganz catheter placement and subsequently at approximately 2 hours (54 second studies) and 24 hours (29 third studies). Occasionally patients warranted hemodynamic monitoring for longer periods and further studies were obtained.

Each study consisted of hemodynamic measurements that were concurrent with recordings of the echocardiogram and the electrocardiogram and vectorcardiogram. Echocardiograms and electrocardiograms were obtained in rapid sequence during monitored and nonchanging hemodynamics not greater than one hour apart.

Hemodynamics. Pulmonary artery and balloon occlusion pulmonary artery pressures (PCW) were recorded with a balloon tipped (Swan-Ganz) catheter using a Statham P 50 transducer zero referenced to the midaxillary line. Pulmonary capillary wedge pressures were verified by the presence of a characteristic atrial pulse contour as

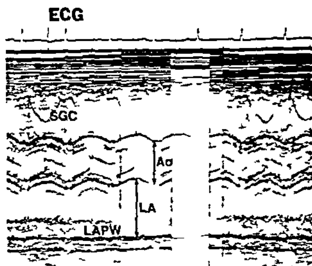


Fig. 1. Echocardiographic recording depicting measurements of left atrial dimension *(LA)* at end-systole *(peak measurement)*, aortic root dimension *(AO* at end-diastole coincident with peak of R wave on the electrocardiographic trace). Measurements shown are from the middle of the lines of aortic wall echoes, and posterior left atrial wall echo, made to the nearest tenth centimeter. (Note importance of damping to eliminate ambiguity regarding structures, especially posterior left atrial wall, *LAPW*.) Echoes from the Swan-Ganz catheter *(SGC)* in this patient are shown.

well as a fall in pulmonary artery mean pressure with balloon inflation and return to the original level with balloon deflation. When triple lumen catheters were placed, right atrial pressure was obtained at each study; otherwise the right atrial pressure was obtained at the time of catheter placement and/or catheter withdrawal. Arterial blood pressure was recorded by cuff or from an indwelling intra-arterial cannula at the time of each study.

Echocardiograms. Echocardiograms were obtained with a commercially available one-dimensional echocardiograph and strip chart recorder (Ekoline 20A, Honeywell 1850A). A 2.25 MHz transducer ½ inch in diameter prefocused at 10 cm and operated at a pulse repetition rate of 1,000 impulses per second was used. All examinations were made with the patient supine and the transducer in the third and fifth intercostal spaces at the left sternal border. Recordings of aortic root, aortic valve leaflets, and left atrium were made.

Careful attention was given to obtain maximally damped tracings in order to minimize ambiguity regarding the true anterior and posterior

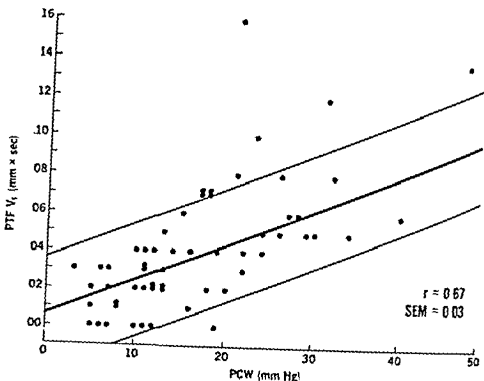


Fig 2 P terminal force in Lead V_1 (*PTF* V_1) plotted against the pulmonary capillary wedge (*PCW*) pressure for 5[illegible] patients on initial study (r = .67) The regression line (*broad line*) shown is represented by the equation PTF V_1 = −.0021 PCW − .0052 with *narrow lines representing ± standard error of the mean*

aortic walls and true posterior left atrial wall[9] A minor sweep of the left atrium was made to obtain the maximum left atrial dimension in the plane of the aortic valve The left atrial dimension was measured at end systole The aortic root dimension was measured at end-diastole at the peak of the R wave on the electrocardiographic trace (Fig 1) Measurements were taken to the nearest tenth centimeter All echograms were read independently by two of the authors (J S G R D B) and were excluded if discrepancies of measurement could not be resolved or if studies were technically inadequate four such studies were excluded Body surface area was determined from a standard nomogram The following measurements and ratios were made for review left atrial dimension (cm) left atrial dimension/aortic root dimension ratio and left atrial dimension/body surface area (cm /M) [1]

Electrocardiogram and vectorcardiogram Standard 12 lead and Frank system x y and z leads were obtained with a three channel recorder (Marquette ECG Data Acquisition Cart) Chest lead placement was marked with indelible ink to insure reproducibility of lead placement in sequential studies

Methods of data acquisition and details of computational procedures have been described previously [3] A Control Data Corporation 3[illegible] digital computer was used to obtain 333 differe[illegible] scalar and vectorial measurements for ea[illegible] record comprising practically all paramete[illegible] previously advocated for analysis of electroca[illegible] diograms The set of P wave measureme[illegible] normally made by this program was augmente[illegible] by P wave amplitudes normalized into eighth[illegible] Analog 12 lead and x y z electrocardiogram[illegible] pulmonary capillary wedge (PCW) pressures an[illegible] left atrial dimensions were stored on magneti[illegible] tape for analysis

The following electrocardiographic measurements were made by hand

P terminal force in Lead V_1 (PTF V_1)—defined as the product of the depth (mm) and duration (sec) of the terminal part of the P wave in Lead V_1 (abnormal PTF V_1 defined by Morris and associates[1] as more negative than −.03 mm sec that is <−.03 mm sec)

P terminal force in orthogonal Lead z (PTF Z)—defined as the product of the height and duration of the terminal part of the P wave in Lead z (mm sec)

P wave duration in Lead II (sec)

P waved duration in simultaneous Leads I II III (sec)

Electrocardiograms were recorded at 50 mm/

Table II Electrocardiographic–hemodynamic correlations (PTF V_1 vs PCW)

	PCW < 10 mm Hg	PCW ≥ 10 mm Hg	PCW ≤ 14 mm Hg	PCW > 14 mm Hg
Abnormal PTF V (< −03 mm sec)	0	30	6	24
Normal PTF V (> −03 mm sec)	11	16	23	4

PCW 10 mm Hg cutoff	PCW 14 mm Hg cutoff
Specificity = 100%	Specificity = 79%
Sensitivity = 65%	Sensitivity = 86%
Positive Predictive Index = 100%	Positive Predictive Index = 80%
Negative Predictive Index = 41%	Negative Predictive Index = 85%

PCW = pulmonary capillary wedge pressure PTF V = p w ve terminal force in Lead V

sec 1 mV/10 mm standardization and inspected with a hand lens to minimize measurement error Electrocardiograms were excluded from the study if discrepant measurements by two of the authors (J S G R D B) could not be resolved by mutual agreement and whenever the P wave was superimposed on the T wave inscription Of the 160 individual studies made nine such studies were excluded from hand measurements of the electrocardiogram and orthogonal electrocardiogram

Definition of statistical terms See appendix

Results

The results are divided into parts I and II Part I termed baseline correlations will deal with interrelations of hemodynamics echocardiography electrocardiography and vectorcardiography as obtained on *only* the initial study for each of the 61 patients Part II termed serial correlations refers to the comparison of sequential studies

Part I—Baseline correlations

Electrocardiographic–Hemodynamic correlations In our sample the PTF V was found to correlate best with left atrial mean pressure as estimated by the pulmonary capillary wedge pressure (r = 67 n = 57) Fifty seven initial studies are shown in Fig 2

An abnormal PTF V (< −03 mm sec) was not encountered when the PCW pressure was less than 10 mm Hg Thus disproportionately low filling pressures could be excluded if the PTF V_1 was abnormal a specificity of 100 per cent for this group The sensitivity however of the abnormal PTF V was only fair at predicting an abnormal PCW pressure (≥10 mm Hg) at 65 per cent A PCW pressure (>14 mm Hg) has been shown to be of value in terms of predicting responses to

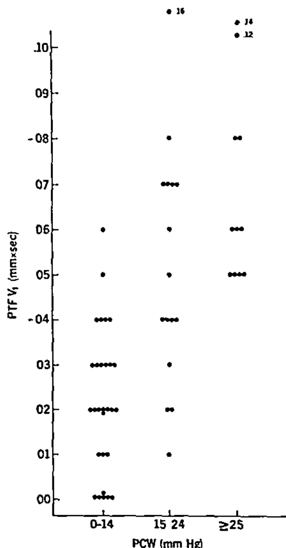


Fig 3 P terminal force in Lead V *PTF V_1* plotted against pulmonary capillary wedge *(PCW)* pressures grouped according to magnitude I (0 to 14 mm Hg) II (15 to 24 mm Hg) and III (25 mm Hg and above) Patients within the normal range or with only minimal elevations of PCW pressure represented by group I infrequently had an abnormal PTF V The six patients with an abnormal PTF V all had enlarged left atrial dimensions normalized for body surface area Also noted is that patients with severely abnormal PCW pressures that is greater than 24 mm Hg invariably had markedly abnormal PTF V (< − 05 mm/sec)

Table III Electrocardiographic–echocardiographic correlations (PTF V_1 vs LA Dimension LA/M² LA/AO ratio)

Echo measurements and indices	% Sensitivity of PTF V_1 for LA enlargement	% Specificity of PTF V_1 for LA enlargement
LA > 5 0 cm	100	53
LA_3 > 4 5 cm	74	59
LA_4 > 4 0 cm.	63	61
LA/M ≥ 2 0	64	92
LA/AO ≥ 1.2	58	48

PTF V = < −03 mm-sec
LA = left atrial diameter LA/AO = left atrial to aortic root dimension index LA/M = left atrial to body surface area index PTF V = p wave terminal force in Lead V

with PCW (Fig 4) This correlation was not improved by correcting left atrial dimension for body surface area (r = 41 n = 59) The correlation between left atrial to aortic root dimension ratio[18] and PCW pressure did not reach statistical significance Indeed there is a wide overlap which prevents use of the echo dimension for indicating the level of wedge pressure for any particular patient

Echocardiographic–Electrocardiographic correlations The correlation between left atrial dimension and PTF V_1 was poor (r = 0 49 n = 56) and not statistically different from the correlation with PTF Z (r = 0 42 n = 52) All other P wave measurements failed to correlate with left atrial dimension at higher than 0 31

Utilizing PTF V_1 statistical indices were computed for various degrees of left atrial enlargement (Table III) As more abnormal left atrial dimensions are selected for comparison the sensitivity of an abnormal PTF V_1 (<−03 mm sec) in suggesting left atrial enlargement is improved This corroborates the findings of Waggoner and colleagues who compared nonsimultaneous electrocardiographic and echocardiographic studies in a larger patient group Specificity of PTF V_1 remains poor only slightly better than 50 per cent for all atrial sizes

Patients with an abnormal PTF V as a group have larger mean left atrial dimensions than patients with a normal PTF V (4 4 cm ± 0 6 cm versus 3 7 cm ± 0.8 cm pNS) The overlapping atrial dimensions in these two groups however are considerable and separation is not possible from knowledge of PTF V

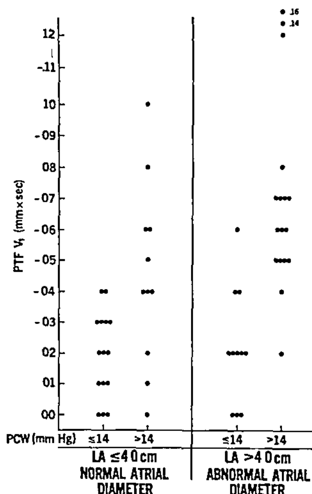


Fig 5 Comparison of patients with normal and abnormal left atrial dimensions with regard to the degree of pulmonary capillary wedge *(PCW)* pressure elevation and the P terminal force in Lead V PTF V For patients with either normal or abnormal left atrial dimensions, the PTF V more closely correlates with the PCW pressure in our patients.

Calculations of atrial wall tension estimated from the following formula

Wall tension = pressure × cavity diameter[6]

Left atrial wall tension (estimate) = PCW pressure × left atrial dimension

were analyzed with respect to all P wave measurements and revealed the highest correlation with PTF V_1 (r = 72 n = 56) This correlation is higher than though not statistically different from that obtained with either PCW pressure or left atrial dimension alone By separation of our patients into two groups according to atrial size (Fig 5) we could demonstrate the predominant contribution of pressure to PTF V

Table IVA Serial correlations Patients lowering their initial PCW pressure 15 per cent

Initial parameters				*Final parameters*				*Changes observed*			
PCW	*LA*	*PTF V*	*PTF Z*	*PCW*	*LA*	*PTF V*	*PTF Z*	*PCW*	*LA*	*PTF V*	*PTF Z*
48	[illegible]5	−14	10	40	50	−13	06	−8	−0.5	+.01	−.04
40	38	−06	0[illegible]	15	[illegible]	−08	08	−2[illegible]	+17	−.0[illegible]	+.03
34	45	−05	03	18	41	−0[illegible]	0[illegible]	−16	−04	0	+.0[illegible]
32	46	−08	10	19	4.8	−08	03	−13	+02	−.07	−0[illegible]
31	47	−12	02	23	42	−14	06	−8	−0.5	−07	+01
30	36	−05	0	17	38	−0[illegible]	02	−13	+0.2	−01	+0[illegible]
29	4.2	−0[illegible]	0	10	3[illegible]	−0[illegible]	06	−19	−07	0	+.06
28	49	−06	0	22	50	−05	0	−6	+01	+01	0
2[illegible]	38	−08	0	15	40	−09	04	−11	+0.2	−01	+04
23	37	−10	0	6	41	−10	04	−17	+04	0	+.04
22	40	−04	0	17	41	−0[illegible]	02	−5	+01	−01	+0[illegible]
22	40	−06	02	1[illegible]	3.8	−02	02	−7	−0.2	+04	0
22	50	−03	02	13	4.2	−03	02	−9	−08	0	0
20	43	−02	0	17	43	−03	03	−[illegible]	0	−01	+.03
19	36	−04	0	6	39	−04	0	−13	+03	0	0
18	39	−02	0	12	39	−02	01	−6	0	0	+.01
18	46	−07	0	8	4.5	−07	0	−10	−01	0	0
18	4.8	−07	05	14	47	−08	02	−4	−01	−01	−.03
17	4.3	−07	06	9	38	−03	02	−8	−05	+.04	−.04
16	34	−01	01	12	30	0	0	−4	−04	+.01	−01
16	3.2	−05	0	10	30	−06	02	−6	−0.2	−01	+.02
15	51	−06	05	12	55	−07	03	−3	+04	−01	−0[illegible]
14	47	−04	02	10	4.5	−04	03	−4	−0.2	0	+01
12	50	−02	03	8	44	−02	03	−4	−06	0	0
11	4.8	−03	01	5	44	−04	02	−6	−04	−01	+01
11	34	−02	0	2	3.2	−04	0	−9	−02	−0[illegible]	0
11	40	−04	03	6	33	−04	02	−5	−07	0	−01
11	31	0	0	7	35	0	0	−4	+04	0	0
10	37	−04	01	3	36	−03	03	−7	−01	+01	+0[illegible]
7	28	−02	02	3	40	−02	0	−4	+1.2	0	−0[illegible]

Designates acute myocardial infarction patients.
LA indicates absolute echo dimension of left atrium (Fig 1)
LA = left atrial dimension PCW = pulmonary capillary wedge pressure PTF V = p wave terminal force Lead V PTF Z = p wave terminal force Lead Z.

Hemodynamic measurements In 32 of our 61 patients we obtained right atrial pressures simultaneously with the PCW measurement The mean right atrial and PCW pressures correlated well (r = 72 n = 32) All but one patient with PCW pressures greater than 14 mm Hg had right atrial pressures greater than 6 mm Hg This was also true of the eight patients with acute myocardial infarction who had right atrial pressures measured In our patient sample elevated PCW pressures often were reflected by an elevated right atrial mean pressure regardless of diagnostic category

Part II—Serial studies Serial studies were available on 52 patients During the period of observation 30 of 52 patients lowered their PCW pressure values by more than 15 per cent (mean fall PCW = 43 per cent) (Table IVA) 18 of [illegible] patients did not alter their baseline PCW pressure importantly (mean change PCW + 15 per cent) (Table IVB) and four of 52 patients increased their PCW pressure importantly (mean elevation PCW = 61 per cent) (Table IVC)

Electrocardiographic–Hemodynamic correlations Of the 30 patients whose PCW pressure was lowered by greater than 15 per cent there was no significant change (pNS n = 30) seen in the PTF V Noteworthy is the response of the PTF V, in those 13 patients with acute myocardial infarction who lowered their PCW pressure by 15 per cent or greater PTF V_1 did *not* change in the majority (7 out of 13) of these patients Three out of 13 were concordant with the wedge pressure change and three out of 13 were discordant with

Table IVB Serial correlations Patients not changing their PCW importantly

Initial parameters				*Final parameters*				*Changes observed*			
PCW	*LA*	*PTF V*	*PTF Z*	*PCW*	*LA*	*PTF V*	*PTF Z*	*PCW*	*LA*	*PTF V*	*PTF Z*
13	4 3	−02	0	15	4 2	−0?	0	+2	−0 1	0	0
6	4 4	0	0	5	4.8	−01	01	−1	+0 4	−.01	+.01
5	2 2	0	0	5	2 1	−01	0	0	−0 1	−.01	0
24	4.5	−.04	04	24	4.5	−0ɔ	0?	0	0	−01	−02
17	5 0	−07	03	19	5 0	−06	04	+2	0	+.01	+.01
13	5 0	−02	01	12	5.3	−03	0?	−1	+0.3	−01	+ 01
17	4 9	†	†	19	3.8	†	†	+2	−1 1	†	†
6	2 9	−03	01	6	2 8	−03	01	0	−0 1	0	0
10	4 7	−04	.03	11	4 6	−05	02	+1	−0 1	−.01	−01
21	4 9	−16	07	20	4 7	−16	.07	−1	−0 2	0	0
5	3 8	−02	01	5	3 8	−03	0	0	0	−.01	−01
10	4 ɟ	−0?	0	10	4 7	−0?	01	0	+0.2	0	+ 01
7	4.2	0	0	6	−	−.01	01	−1	−	−.01	+.01
12	4 1	0	0	15	3 6	−04	0	+3	−0.5	−04	0
12	3 4	−04	03	14	3 4	−.02	03	+2	0	+ 02	0
27	5.2	−06	03	32	5 2	−0ɔ	04	+5	0	+.01	+ 01
5	3 3	−.01	01	10	3 4	0	0	+5	+0 1	+ 01	−01
3	3.5	−03	03	6	3 5	−0?	.02	+3	0	+.01	−.01

†Designates P wa e superimposed on T wa

LA = l ft tri l dimension PCW = pulmonary capillary wedge pressure PTF V = p wave terminal f rce in Lead V PTF Z = p wav terminal force in Le d Z.

Table IVC Serial correlations Patients increasing their initial PCW pressure importantly

Initial parameters				*Final parameters*				*Changes observed*			
PCW	*LA*	*PTF V*	*PTF Z*	*PCW*	*LA*	*PTF V*	*PTF Z*	*PCW*	*LA*	*PTF V*	*PTF Z*
11	2 7	−03	03	16	3 4	−06	06	+5	+0 7	−03	+.03
7	3 9	−03	02	14	3 5	−04	03	+7	−0 4	−01	+ 01
24	4 6	−.05	03	37	4 6	−05	02	+13	0	0	−01
13	5 6	−05	03	19	5 6	−0ɔ	0?	+6	0	0	−01

LA = left atrial dimension PCW = pulmon ry c p llary wedge pressure PTF V = p wav terminal force in Lead V PTF Z = p wave terminal force in Lead Z.

the wedge pressure change (Table IVA) Correlations of other hand P wave measurements including PTF Z and P wave duration did not achieve statistical significance

Computerized vectorcardiographic analysis revealed a low correlation which achieved statistical significance between the falling PCW pressure and the z component of the P wave spatial maximum vector* (r = 45) No significant correlations were obtained for other computer measured vectorcardiographic P wave parameters

*Refers to the mpute m asurement f the m im m P wa ect in space projected l ng orthogon l Lead z. A d ta led list of these P w e measurements has bee p bl..hed

Echocardiographic–Hemodynamic correlations We observed no significant change in the left atrial dimension despite the mean fall in PCW pressure of 43 per cent in this group of patients In fact these patients behaved indistinguishably from those patients with no significant alteration of the PCW pressure in sequential study (Table IVB) or from those patients increasing their wedge pressure on sequential study (Table IVC)

Hemodynamics A significant correlation was demonstrated between the fall in PCW pressure and the change in pulmonary artery systolic pressure (r = 76 n = 18) as well as the change in

the right atrial mean pressure ($r = 60$ $n = 17$, $p < 02$)

Discussion

This study has examined the combined use of new diagnostic modalities to investigate the hemodynamic and anatomic correlations of established electrocardiographic criteria employing the P wave as a model Secondly it has investigated the usefulness of the electrocardiographic P wave criteria in predicting physiologic changes in cardiologically unstable patients Thirdly comparison was made of vectorcardiographic and scalar electrocardiographic analysis of the P wave using dynamic anatomic and hemodynamic parameters as a basis for this analysis

The results of this study indicate that the ECG pattern of left atrial overload from standard Lead V_1 is significantly but only moderately correlated with mean left atrial pressure and poorly correlated with left atrial size in cardiac intensive care patients The correlation of the ECG pattern is somewhat improved by using the product of left atrial size and pressure an expression for left atrial wall tension While the data allow one to use P terminal negativity to classify patients with extremes of left atrial pressure before acute therapeutic interventions also found by others[21,22] the correlations obtained do not permit accurate prediction of left ventricular filling pressure from the electrocardiographic and echocardiographic parameters studied This inability to freely extrapolate from the magnitude of the P terminal negativity to left ventricular filling pressure suggests that additional factors such as interatrial conduction and type and duration of left atrial hypertension are responsible for inscription of the P wave

That our data and those of others[2,27,28] fail to show good correspondence of electrocardiographic left atrial abnormality with increased left atrial size or left atrial pressure while other studies[3,5,6] have demonstrated this may reflect differences between the size and diagnostic category of patient samples duration of left atrial hypertension and presence or absence of other factors including functional or structural abnormalities affecting the interatrial conduction time From a recent study by Josephson and associates[7] the one parameter that showed a consistent relation to the left atrial *overload* pattern was the presence of a prolonged interatrial conduction time It was the feeling of these authors that the interatrial conduction time was the intracardiac counterpart of the surface ECG pattern of left atrial overload and that multiple causes might produce this abnormality

A second conclusion of this study is that acute changes in the PCW pressure are neither predicted by manual or computer assisted observation of concurrent P wave morphology nor by measurement of the echocardiographic left atrial dimension This suggests that either the electrocardiographic atrial abnormality is incapable of responding rapidly to changes in left atrial pressure or that other factors determine this ECG abnormality independently of left atrial pressure The rarity of the left atrial overload pattern with low pressure and its consistent presence with high pressures lead us to the former possibility Two studies which have strictly limited the diagnostic category to acute myocardial infarction or severe angina pectoris and excluded patients with chronic conditions such as hypertension and congestive heart failure have shown concordant changes in the PCW pressure and the PTF V_1 in most instances[1,2] These findings may not be applicable to the wider cardiac intensive care population Although for our patient group left atrial dimension contributes relatively little to PTF V_1 compared with left atrial pressure six patients (Fig 3) did have enlarged left atria abnormal P terminal forces but *normal* PCW pressures One may speculate that an enlarged left atrium is a marker for previous left atrial hypertension and hence the left atrial overload pattern It is also possible that pathologic changes in the left atrial wall occurring with left atrial dilatation affected interatrial conducting pathways so as to prolong intra atrial conduction Increased left atrial dimension may be accompanied by lower mean left atrial pressure without affecting the left atrial overload pattern this represents a false positive prediction of the left ventricular filling pressure from the ECG This may explain why some investigators have found correlations with PTF V_1 and atrial size in rheumatic mitral valvular disease more commonly than other diagnostic categories[1,20]

It is apparent that neither the electrocardiogram which reflects mean spatial and temporal relations of cardiac electrical activity nor atrial size determined by echocardiogram can be relied

upon to reflect the left ventricular filling pressure accurately enough to preclude its direct measurement

Electrocardiographic P wave criteria whether scalar or orthogonal manual or computer assisted at best showed only a moderate correlation with concurrent measurements of left atrial pressure and size suggesting that inferences from the electrocardiogram to hemodynamics and anatomy be carefully cautioned The less specific term left atrial overload rather than enlargement or hypertension seems appropriate in referring to increased terminal posterior forces of the P wave

Summary

Combining electrocardiography with current techniques for continuous bedside hemodynamic monitoring and echocardiography permits analysis of P wave morphology in light of concurrent and accurate measurements of left atrial pressure and chamber size In order to determine a noninvasive means of estimating left ventricular filling pressure during changing hemodynamics and to evaluate contributions of left atrial size and pressure to P wave morphology 144 pulmonary capillary wedge pressures (PCW mm Hg) with 12 lead electrocardiograms vectorcardiograms and left atrial echocardiograms were obtained in 61 cardiac care patients

Noninvasive predictors of the PCW were sought initially and after changes in the PCW Three electrocardiographic and seven vectorcardiographic P wave indices and three echocardiographic left atrial dimension indices were evaluated This study found that the P terminal negativity PTF V_1 (abnormal defined as greater than -03 mm sec negativity) was the best electrocardiographic predictor of PCW PTF V correlated moderately well with PCW ($r = 67$ $P < 01$) and was the best separator of patients with PCW ≤ 14 mm Hg from those with PCW > 14 (sensitivity 86 per cent and specificity 79 per cent) Despite the lack of a high correlation PTF V was helpful in that a normal PTF V_1 excluded patients with PCW pressures in the pulmonary edema range (PCW > 24 mm Hg) No patient with PCW > 24 had a normal PTF V Similarly presence of an abnormal PTF V excluded patients with low left ventricular filling pressures (PCW < 10 mm Hg) Neither P terminal positivity in orthogonal lead z nor a multiple coefficient regression program of computer measured vectorcardiographic parameters was superior to other individual electrocardiographic and vectorcardiographic measurements in their correlation with PCW Despite the widespread use of PTF V for the electrocardiographic diagnosis of left atrial enlargement echocardiographic left atrial dimension showed a significant but low correlation with PTF V_1 ($r = 49$) suggesting that atrial size is a weaker determinant of PTF V_1 than atrial hypertension Left atrial wall tension expressed as the product of PCW pressure and left atrial dimension also showed a moderate though better correlation ($r = 72$) with PTF V_1 than did PCW pressure or left atrial dimension individually Conclusions of this study are that additional factors are importantly related to the ECG pattern of left atrial overload This conclusion is supported by the rather modest correlation coefficient between PTF V_1 and PCW pressure initially and an important second finding that in 51 patients studied serially simultaneous changes in the electrocardiogram vectorcardiogram and left atrial dimension were unreliable predictors of acute changes in PCW pressure

The study design utilized offers potential for testing and improving current electrocardiographic criteria and the results obtained caution against inferences made about hemodynamics and cardiac anatomy from the electrocardiogram particularly when non-dynamic comparisons between the electrocardiogram and these functions are made

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Appendix

Definition of statistical terms The following terms are according to standard usage [24] *True positives*—those patients with positive tests who also have the abnormality sought by the test *False negatives*—those patients with negative tests but who have the abnormality sought by the test *True negatives*—those patients with negative tests and who lack the abnormality sought by the test and *False positives*—those patients with positive tests but who lack the abnormality sought by the test

Additional terms are defined as follows [24]

$$\% \text{ Sensitivity} = \frac{\text{True positives}}{\text{True positives} + \text{False negatives}} \times 100$$

$$\% \text{ Specificity} = \frac{\text{True negatives}}{\text{True negatives} + \text{false positives}} \times 100$$

$$\text{Positive Predictive Index} = \frac{\text{True positives}}{\text{All positive tests}} \times 100$$

$$\text{Negative Predictive Index} = \frac{\text{True negatives}}{\text{All negative tests}} \times 100$$

The addition of predictive indices to the standard terms facilitates complete understanding of a test s value It allows an understanding of how reliable a positive or negative test is in estimating the abnormality sought Unlike either sensitivity

or specificity it compares all patients with positive or negative tests to assess whether a test is more helpful when positive or negative This can be seen from results in Table II where it is evident that if we have a normal PTF V_1 i e a negative test, we have only a 41 per cent probability of identifying a normal PCW (<10 mm Hg)—a poor test indeed yet looking at a positive test virtually assures us that pressures are abnormal (>10 mm Hg) information that is not readily available from assessment of sensitivity and specificity or the coefficient of correlation Product-moment correlation coefficient r values are computed from comparison between parameters and are given when they exceed the 0 01 critical level of significance

Contrasting effects of acute beta blockade with propranolol on plasma catecholamines and renin in essential hypertension a possible basis for the delayed antihypertensive response*

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Although propranolol as well as other β adreno receptor antagonists has been found to be an effective antihypertensive drug after some ten years of usage the mechanisms by which it lowers blood pressure are still not fully clarified [1] For a variety of reasons none of the theories propounded up to now is considered completely satisfactory However since cardiac and renin blockade are common properties of almost all the antihypertensive beta blockers the conviction that these actions are responsible for the hypotensive effect is widely held One point that the so-called cardiac and "renin theories fail to explain fully is the dissociation in time between the decrease in cardiac output and renin which can be shown acutely with intravenous infusions and the delayed hypotensive effect which is said to follow only chronic treatment Hemodynamic studies in normotensive and hypertensive patients have shown that after acute infusion of propranolol blood pressure is unchanged while cardiac output decreases and peripheral resistance increases The latter effect has been attributed to blockade of vascular β receptors leading to a prevalent α tone and thus to a vasoconstriction which is supposed to counteract the reduction in cardiac output [4] However two considerations cast doubt on this interpretation first the infusion of propranolol intraarterially in man does not induce vasoconstriction, and second the β_1 selective antagonists although devoid of activity on the β vascular receptors, cause acute changes in cardiac output and peripheral resistance indistinguishable from those induced by the non selective β_1 and β antagonists [3]

These observations suggest that a simple unmasking of α tone by blockade of vascular β receptors is an inadequate explanation for the vasoconstrictor effect of acute β blockade In order to examine whether and to what extent the sympathetic nervous system is affected by acute β blockade in hypertensive patients at rest, we have evaluated the changes in plasma norepinephrine and epinephrine induced by intravenous infusion of propranolol at the same time we have determined changes in plasma renin activity and heart rate as indices of the cardiac and renin-angiotensin system blockade

Methods

Eleven hospitalized patients with essential hypertension, seven females and four males aged 26 to 57 years were included in the study which was conducted with the approval of the Comm

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Table I Effects of intravenous infusion of 0.12 mg/Kg propranolol on blood pressure, heart rate, plasma renin activity, plasma norepinephrine and plasma epinephrine (mean ± S.E.M., n = 11)

	Control	*15 min*	*30 min*	*45 min*	*60 min.*
Mean B.P. (mm Hg)	119 ± 5	120 ± 6 N.S.	121 ± 6 N.S.	120 ± 6 N.S.	121 ± 7 N.S.
H.R. (beats/min.)	76 ± 2.2	65 ± 1.9 p < 0.001	66 ± 2.1 p < 0.001	66 ± 2.2 p < 0.001	66 ± 1.9 p < 0.001
P.R.A. (ng/mL/hr.)	2.7 ± 0.76	2.0 ± 0.54 p < 0.05	1.7 ± 0.49 p < 0.01	1.5 ± 0.42 p < 0.01	1.4 ± 0.38 p < 0.01
N.E. (pg/mL)	243 ± [illegible]6	275 ± 25 N.S.	345 ± 28 p < 0.001	323 ± 29 p < 0.001	3[illegible]6 ± 32 p < 0.005
E. (pg/mL)	35 ± 7.4	56 ± 11.3 p < 0.01	57 ± 11.4 p < 0.01	5[illegible] ± 13.0 p < 0.01	6[illegible] ± 15.6 p < 0.01

tee of Human Rights in Research. Secondary causes of hypertension were excluded by appropriate methods in all cases. All patients were free of any other associated disease or complication related to hypertension and at the moment of study were on a constant sodium intake (100 mEq Na/day) for at least 4 days; none of them had received any antihypertensive treatment for at least 2 weeks before the studies.

Studies were performed in the morning between 9 and 12 noon according to the following protocol. Patients were admitted to a quiet room and were put in the supine position while a slow intravenous infusion of 0.9 per cent NaCl solution was set up for sampling and infusion of propranolol. The volume of saline infused throughout the studies was equal to that of collected blood. After 60 minutes in the supine position, baseline heart rate and sphygmomanometric arterial pressure (at least five readings) were recorded and baseline blood samples were collected. Immediately after blood collection propranolol HCl in a dosage of 0.12 mg/Kg was infused intravenously over five minutes under constant ECG control; subsequently blood samples were collected 15, 30, 45 and 60 minutes after the beginning of the infusion. Throughout the studies heart rate and blood pressure were measured every 2 minutes. Mean blood pressure was calculated by adding ⅓ of pulse pressure to diastolic values. Plasma renin activity was determined by radioimmunoassay of angiotensin I after incubation of plasma in the presence of angiotensinase inhibitors according to the method of Sealey and colleagues. Plasma norepinephrine and epinephrine were determined by radioenzymatic assay according to the technique of Passon and Peuler in the Upjohn laboratory. The limit of sensitivity of this method is 5 and 3 pg, respectively, for norepinephrine and epinephrine. Plasma propranolol concentrations were determined using the fluorometric method of Shand and co-workers.[15]

Results are expressed as mean ± standard error of mean. Significance was tested by Student's t test for paired data, each subject providing his own control data.

Results

Table I reports our results. After propranolol mean blood pressure remained unchanged while systolic pressure showed an insignificant decrease and diastolic manifested an insignificant increase. Heart rate decreased by 14 per cent within the first 15 minutes and remained unchanged thereafter. Mean plasma renin activity, whose control values ranged from 0.5 to 7.4 ng/ml/hr, after propranolol showed a progressive decrease which was maximal (48 per cent) at 60 minutes. Baseline norepinephrine levels varied between 113 and 403 pg/ml and those of epinephrine between 13 and 93 pg/ml; after propranolol norepinephrine increments at 30, 45, and 60 minutes (respectively 102 ± 20, 80 ± 17 and 83 ± 23 pg/ml) and those of epinephrine at 15, 30, 45, and 60 minutes (respectively 21 ± 6.5, 22 ± 6.9, 22 ± 6.9, and 30 ± 9.6 pg/ml) were all statistically significant.

Plasma propranolol concentrations, measured in five studies 30 minutes after propranolol, ranged from 19 to 41 ng/ml. These levels are close to those reported by Shand and co-workers[5] under similar experimental conditions.

Discussion

This study shows that within an hour after intravenous propranolol plasma norepinephrine and epinephrine were significantly higher than the control value. It has been reported that

plasma catecholamine levels may be raised by even mildly stressful procedures such as venipuncture and simply by anxiety [18,19] however in our protocol venipuncture preceded the baseline blood collection by 60 minutes and this period of time should have been sufficient to achieve basal catecholamine levels Similar resting periods are considered sufficient to achieve basal levels of plasma renin activity [19] As to the anxiety factor the time course of norepinephrine and epinephrine increases makes it unlikely that the changes were related to apprehension particularly considering the total absence of subjective changes following propranolol infusion Finally in three patients the infusion of 10 ml of saline instead of propranolol did not induce any consistent change in plasma catecholamines Since propranolol does not affect the radioenzymatic assay of catecholamines it is unlikely that the observed changes are related to a methodological artifact

The effect of propranolol on plasma norepinephrine and epinephrine could be due to its pharmacological properties or to some indirect mechanisms stimulated by the hemodynamic or humorally induced changes In rats propranolol has been shown to induce a release of adrenal catecholamines which is due to its anesthetic properties At very high concentrations propranolol has been reported to inhibit reuptake of norepinephrine in vitro but more recent studies have shown that at concentrations more similar to those attained in our studies this effect is negligible Since propranolol is a highly lipid soluble drug and can rapidly achieve partition between brain and plasma the changes observed in catecholamine levels might be due to its action on the central nervous system However Lewis and Haeusler infusing propranolol intravenously in rabbits at concentrations comparable to those of our studies showed a decrease in preganglionic nerve activity this experiment suggests that propranolol should have on the central nervous system an inhibiting rather than a stimulating action In addition it has been shown in vitro that propranolol might have some adrenergic neuron blocking activity Finally if we assume the existence of β adrenoreceptor mediated positive feedback mechanism for norepinephrine release at the adrenergic nerve endings [8] propranolol should again induce a fall in norepinephrine release

In all with the exception of a possible effect on adrenal catecholamines the direct pharmacological actions of propranolol should cause a decrease rather than a rise in catecholamines thus, to explain our results we suggest that the acute β blockade stimulates by some indirect or reflex mechanism an increase in sympathetic nervous system activity of such magnitude to override the eventual sympatholytic effects of the drug Irving and associates[31] reported an increased adrenergic response to exercise in β blocked individuals this observation was interpreted as a compensatory response to a smaller rise of cardiac outp t leading to a lower blood pressure during exercise. This interpretation does not apply to our model, as no changes in blood pressure were observed However it is possible that the fall in cardiac output without changes in blood pressure either dependent on the decrease in heart rate or stroke volume may be a sufficient stimulus to induce an increase in sympathetic nervous system activit

As the decrease in renin release indicates a decrease in angiotensin II formation the possible influence of such decrease on the centra' -- peripheral nervous activity should also be cor ered however since angiotensin II has l shown to facilitate norepinephrine release f the neural endings by enhancing its biosynth and reducing its reuptake [3, 34] to stimulate c cholamine release from the adrenal gland[35] an increase the central adrenergic outflow [1] it se unlikely that the acute blockade of renin rel would contribute to the increase of plasma c cholamines

For these reasons we suggest that the imi diate hemodynamic changes induced by propr olol are the main requirements to elicit t sympathoadrenergic response

Although the present study does not define t duration of the acutely induced increase in ca cholamines the available evidence suggests th it is transient since it has not been described wi the long term use of propranolol [4] Thus t increase in sympathetic nervous activity m explain the delay in onset of the antihypertensi action of propranolol indeed if the absence immediate hypotensive effect during acute inf sion is due to the increase in catecholamines th effect is likely to counteract in the short term th cardiac and renin suppressing actions of be blockade but it would be expected to be transien for two reasons First prolonged infusion of no

epinephrine produces only a transient rise of arterial pressure and second because cardiovascular reflexes tend to show adaptation with time[41] once the increased sympathetic activity wears off the hypotensive effect related to the cardiac and renin blockade would be exposed This hypothesis is in keeping with recent studies with propranolol which indicate that at least part of its hypotensive effect can occur within a few days or even hours[3, 5] Accordingly an initial mechanism of action of propranolol might be proposed that involves a decrease in cardiac and renin activities This action does not exclude the possibility of further hypotensive mechanisms dependent upon the direct effects on the central nervous system or upon the reduction of the excitatory afferent input to the central nervous system or finally upon the interference with the presynaptic feed back mechanism mentioned above

Summary

Blood pressure heart rate plasma renin activity plasma norepinephrine and plasma epinephrine were determined in 11 patients with essential hypertension at rest before and 15 30 45 and 60 minutes after an intravenous infusion of 0 12 mg/Kg propranolol given over five minutes After propranolol mean blood pressure was unchanged heart rate decreased by 14 per cent within 15 minutes and showed no further changes Plasma renin activity decreased progressively by 48 per cent 60 minutes after propranolol whereas plasma norepinephrine and epinephrine were always higher after propranolol than control values Increases in norepinephrine were statistically significant at 30 45 and 60 minutes (respectively 49 39 and 45 per cent $P < 0.005$ at least) and those of epinephrine even at 15 minutes (respectively 60 82 62 and 94 per cent $P < 0.01$ for all)

These results indicate that acute beta blockade with propranolol induces increases in circulating plasma norepinephrine and epinephrine which might be consequent to rapidly induced hemodynamic changes This augmented sympathetic activity might explain why propranolol when acutely infused does not decrease blood pressure despite effective cardiac and renin blockade

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Use of oral prazosin hydrochloride in congestive failure following acute myocardial infarction

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The consequences and clinical manifestations of congestive heart failure can be related to reduction in cardiac output and elevation of pulmonary and systemic venous pressures Conventional treatment attempts to improve cardiac output and alleviate pulmonary congestion by means of positive inotropic agents such as digoxin combined with diuretics

In acute myocardial infarction this treatment has the disadvantage of potentially increasing myocardial oxygen demands electrical toxicity occurs more easily and the hemodynamic response to digoxin is reduced and inconsistent since the normal myocardium is already operating at near peak level of contractility

In contrast in acute myocardial infarction reducing impedance to left ventricular ejection with nitroprusside or phentolamine may improve cardiac output and reducing the preload with systemic venous dilators such as nitroglycerin or isosorbide dinitrate or nitroprusside relieves pulmonary congestion In both cases myocardial oxygen requirements may diminish This makes peripheral vasodilators the preferred drugs for the treatment of heart failure in acute myocardial infarction

The purpose of this study is to evaluate the hemodynamic effects of a new vasodilator prazosin in patients with severe left heart failure during acute myocardial infarction

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Prazosin with venous and arterial dilating properties has already proved to be useful in the treatment of refractory chronic heart failure its action being similar to that of nitroprusside but it has not yet been used in acute myocardial infarction

Materials and methods

The hemodynamic effect of 2 5 to 7 mg of oral prazosin in a single dose was studied in 11 patients with acute myocardial infarction and severe left heart failure Nine were men and two women aged 58 ± 13 years

Each patient had clinical electrocardiographic and laboratory evidence of acute myocardial infarction in eight cases it was anterolateral in two inferoposterior and in one case it was inferior and anterior All the studies were performed during the first second or third day after the onset of symptoms All the patients had clinical signs of severe cardiac dysfunction such as dyspnea at rest orthopnea rales and third heart sound seven of them had radiologic evidence of acute pulmonary edema and five showed some signs of low output oliguria cold clammy skin or impaired mental function All of them were in subsets II or IV according to the Forrester classification Four patients had previously been treated with nitroprusside for several hours and two with diuretics

The patients were carefully selected excluding those with peak systolic blood pressure inferior to 130 mm Hg as well as the patients submitted to another drug at the time of the study

Right heart catheterization was performed at admission by inserting a Swan Ganz thermodilu

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Table I Prazosin—hemodynamic effect in congestive heart failure following acute myocardial infarct

	Control	1/2 hr		1 hr		2 hr		3 hr	
	n = 11	n = 11	P<	n = 11	P<	n = 11	P<	n = 11	P
HR	93.9 ± 13.7	91.5 ± 14.5	NS	93.9 ± 14.[illegible]	NS	9[illegible].3 ± 13.5	NS	94.7 ± 14.0	[illegible]
CI	2.38 ± 0.42	2.80 ± 0.62	0.0[illegible]	2.96 ± 0.37	0.002	2.80 ± 0.60	0.05	2.9[illegible] ± 0.5[illegible]	00
SI	24.7 ± 4.1	30.[illegible] ± 9.3	0.05	32.6 ± 8.2	0.01	30.2 ± 8.5	0.05	31.5 ± 8.[illegible]	00
RAP	12.5 ± 4.6	8.6 ± 3.9	0.0[illegible]	[illegible].8 ± 5.6	0.005	5.6 ± 5.3	0.002	4.4 ± 5.0	00
PCI	29.8 ± 6.8	23.5 ± 8.5	0.05	19.1 ± 7.5	0.002	18.1 ± 6.9	0.00[illegible]	15.7 ± 7.[illegible]	00
BP	114.2 ± 13.6	103.3 ± 16.0	NS	96.8 ± 13.6	0.00[illegible]	90.9 ± 10.5	0.001	88.7 ± 7.3	00
SVR	3,548 ± 619	2,813 ± 678	0.01	2,450 ± 408	0.001	2,459 ± 408	0.001	2,136 ± 40[illegible]	00
TPR	1,287 ± 414	929 ± 427	0.05	712 ± 3[illegible]8	0.02	707 ± 320	0.002	611 ± 305	00
SWI	48.3 ± 11.2	[illegible]1.6 ± 12.7	NS	[illegible]1.4 ± 13.2	NS	45.4 ± 14.5	NS	46.1 ± 14.0	N
NWI	38.5 ± 11.2	44.5 ± 13.6	NS	43.4 ± 13.3	NS	38.3 ± 13.9	NS	39.5 ± 12.9	N
DWI	9.8 ± 1.8	9.2 ± 2.4	NS	8.0 ± 2.3	0.05	7.1 ± 2.5	0.001	6.6 ± 2.8	00
NWI/SWI	0.79 ± 0.06	0.81 ± 0.07	NS	0.83 ± 0.07	NS	0.84 ± 0.07	0.05	0.85 ± 0.0	00
MPG	6[illegible].6 ± 16.5	63.7 ± 18.4	NS	64.1 ± 15.8	NS	59.8 ± 10.6	NS	61.[illegible] ± 10.3	N
HR × SBP	14,489 ± 2,415	12,799 ± 2,969	NS	11,776 ± 2,713	0.01	11,439 ± 2,456	0.005	10,89[illegible] ± 1,805	00

Abbreviations HR = heart rate in beats/min CI = cardiac index in liters/min/M SI = stroke index in mL/beat/M RAP = mean right a[trial] pressure in mm Hg PCI = mean pulmonary capillary pressure in mm Hg BP = mean blood pressure in mm Hg SVR = systemic vas[cular] resistances in dynes/sec/cm /M TPR = total pulmonary resistances in dynes/sec/cm /M SWI = left ventricular stroke work index gm/beat/M NWI = left ventricular net work index in gm/beat/M DWI = left ventricular diastolic work index in gm/beat/M MPG = [myo]cardial perfusion gradient (aortic diastolic — pulmonary capillary pressure) in mm Hg HR × SBP = heart rate × systolic blood pressure

tion catheter into the pulmonary trunk Right atrial, pulmonary artery and pulmonary capillary wedge pressures were recorded through a Hewlett Packard 1280 transducer in a Siemens Elema Mingograph 34 at a paper speed of 25 mm/sec Cardiac output was determined by thermodilution using an Edwards 9500 computer Arterial blood pressure was measured by arm cuff in mm Hg

Common hemodynamic parameters were calculated according to well known formulas and are summarized in Table I

All parameters were measured at control ½ 1 2 3 6 and 12 hours after a single oral dose of prazosin ranging between 2.5 and 7 mg depending on the body surface area of each patient We could not obtain hemodynamic data after 12 hours in one patient because prazosin effect disappeared after 6 hours and another drug was administered

The paired Student t test was used for the statistical analysis of this data A probability (P) value of less than 0.05 was considered significant

Results

The hemodynamic data before and ½ 1 2 3 6 and 12 hours after oral prazosin are summarized in Table I as well as the P values comparing the hourly determinations with the control values One patient was excluded from the 12 hour determinations and we show the data of the remaini[ng] 10 cases

Hemodynamic effects Heart rate remain[ed] unchanged throughout the 12 hours of measu[re]ments following prazosin administrati[on] (Fig 1)

Cardiac index increased from 2.38 ± 0.[42] liters/min/M during control to 2.8 ± 0.[6] liters/min/M ½ hour after prazosin administr[a]tion ($P < 0.05$) Maximum improvement o[c]curred at 1 hour 2.96 ± 0.30 liters/min/M ($P < 0.002$) (Fig 1) and remained statisticall[y] elevated during 6 hours reaching control valu[es] again 12 hours after prazosin intake Only o[ne] patient showed a transient decline in cardi[ac] output during the study It was due to excessi[ve] pulmonary capillary pressure reduction (Fig 2) i[n] a patient with only moderately elevated capillar[y] pressure at control

As the heart rate did not change the strok[e] index showed a similar enhancement (Fig 1)

Oral prazosin resulted in an important an[d] sustained decline in right atrial pressure fro[m] 12.5 ± 4.6 at control to 8.8 ± 3.9 mm Hg 3[0] minutes after prazosin ($P < 0.05$) Its maximum effect was three hours later (4.4 ± 5.0 mm H[g]) ($P < 0.001$) (Figs 2 3 4 and 5) The effect wa[s] still evident 12 hours after prazosin intake 7.9 ± 2.6 mm Hg ($P < 0.01$) Pulmonary capil[-]lary pressure was markedly elevated before prazo[-]sin (29.8 ± 6.8 mm Hg) and suffered an impor[tant]

6 hr		12 hr	
n = 11	P<	n = 10	P<
93 6 ± 14 9	NS	92 2 ± 10 5	NS
2 81 ± 0 55	0 02	2.60 ± 0 70	NS
30 5 ± 7 4	0.02	29 0 ± 8.3	NS
5 4 ± 4 0	0 001	7 9 ± 2.6	0 01
1 0 ± 6 8	0 001	22.2 ± 8 0	0 002
95 8 ± 9 9	0.002	109 1 ± 14 7	NS
2, 70 ± 605	0 005	3,093 ± 724	NS
771 ± 390	0 005	888 ± 373	0 0[illegible]
47 4 ± 12.1	NS	52 0 ± 15 8	NS
40 6 ± 12.1	NS	43 7 ± 15 6	NS
6.7 ± 2 [illegible]	0 002	8 2 ± 2 4	NS
0 85 ± 0 07	0 02	0 83 ± 0 07	NS
66 4 ± 11 4	NS	68 1 ± 14 0	NS
11 307 ± 2,279	0 005	12 747 ± 2,210	NS

tant and sustained reduction 3 hours later (15 7 ± 7 2) (P < 0 001) This marked decline persisted 6 hours later (Fig 3) rising again 12 hours *after prazosin* (22 2 ± 8 0 mm Hg) (P < 0 05) without reaching control values

One patient had papillary muscle dysfunction with severe mitral regurgitation and a prominent v wave which disappeared 12 hours after prazosin (Fig 4)

Simultaneously mean pulmonary trunk pressure fell from 36 7 ± 8 3 mm Hg to a maximum decrease of 21 4 ± 8 8 mm Hg (P < 0 001) 3 hours later and the decline was still evident 12 hours after prazosin 29 0 ± 9 3 mm Hg (P < 0 05) (Figs 3 4 and 5)

One patient showed pulmonary pulsus alternans which disappeared 3 hours after prazosin intake and reappeared 12 hours later

Systemic arterial mean blood pressure declined in every patient following prazosin ingestion Thus control mean blood pressure of 114 ± 13 6 mm Hg was significantly reduced to 96 8 ± 13 6 mm Hg (P < 0 005) one hour after prazosin administration with maximum reduction 3 hours later 88 7 ± 7 3 mm Hg (P < 0 001) and remained significantly reduced after 6 hours (Fig 6) 95 8 ± 9 9 mm Hg (P < 0 001) but without statistical differences after 12 hours 109 ± 14 7 mm Hg (NS) As patients with elevated blood pressure were selected for this study we found no excessive blood pressure reduction in any of them

Total systemic vascular resistances decreased from 3 548 ± 619 dynes/sec /cm /M at control to 2 813 ± 678 dynes/sec /cm /M 30 minutes later (P < 0 001) and to 2 450 ± 408 one hour after prazosin (P < 0 001) This statistically marked reduction was maintained for 2 and 3 hours After 6 hours the systemic resistances rose again to 2 720 ± 605 dynes/sec /cm ⁵/M (P < 0 01) (Fig 6) and 12 hours later there were no differences compared with control values

Total pulmonary resistances suffered the same reduction from 1 287 ± 414 dynes/sec /cm / M to a maximum decline of 611 ± 305 dynes/sec /cm ⁵/M (P < 0 001) 3 hours after prazosin intake (Fig 6)

The stroke work index and net work index remained unchanged throughout the 12 hours of measurement following administration of prazosin (Fig 7) while the diastolic work index declined from 9 8 ± 1 8 to 7 1 ± 2 5 grammeters/beat/M at 2 hours (P < 0 001) and remained so 6 hours after prazosin

The net/stroke work index quotient increased from 0 79 ± 0 06 to 0 84 ± 0 07 (P < 0 05) 2 hours *after prazosin*

The myocardial perfusion gradient values remained unchanged but with marked individual differences and the systolic blood pressure × heart rate product estimated as a myocardial oxygen consumption index decreased from control values of 14 489 ± 2 414 to 10 892 ± 1 805 (P < 0 001) 3 hours after prazosin intake

Prior to prazosin six patients were in subset II and five in subset IV according to Forrester s hemodynamic classification After prazosin five patients from subset II passed to subset I and one passed to subset III The five patients in subset IV improved two passed to subset I and three to subset II

Discussion

I Hemodynamic effects This investigation demonstrates that when prazosin is given to patients with acute myocardial infarction and severe heart failure it exerts an important and prolonged dilating action on both arterial and venous systems reducing afterload as well as preload Preload reduction is manifested by the decline in pulmonary wedge pressures (P < 0 001) (Table I Figs 2 3 4 and 5) and afterload reduction by the decline in blood pressure and systemic vascular resistances (0 < 0 001) (Table I and Fig 6) The enhancement of cardiac output and stroke index is a consequence of afterload reduction Similar results have been found in patients with chronic congestive heart failure without myocardial

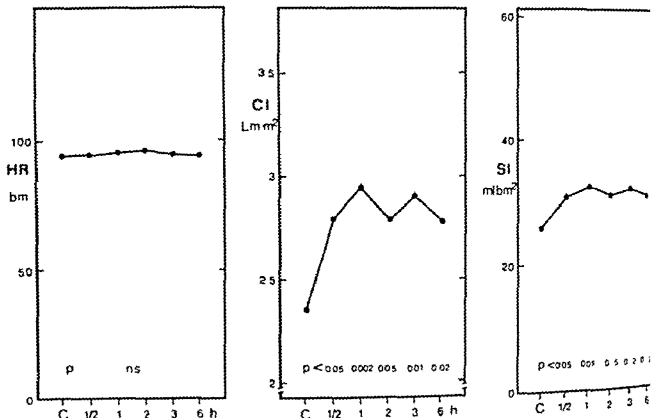


Fig 1 Changes in heart rate (*HR*) cardiac index (*CI*) and stroke index (*SI*) ½ 1 2 3 and 6 hours after a single oral dose of prazosin in 11 patients with acute myocardial infarction and congestive failure C = control values (mean ± standard deviation)

infarction in the few reports about prazosin found in the medical literature

We could not find any change in left ventricular stroke work index or net work index but diastolic work index (wasted energy) decreased (Table I and Fig 7) and the net/stroke work index quotient improved indicating better utilization of heart energy

Every patient in this study was in severe congestive failure all of them included in subsets II and IV of the Forrester hemodynamic classification and seven had clinically acute pulmonary edema Prazosin effect is quite uniform but shows important individual differences For this reason its action is unpredictable and this drug must be used only in patients with blood pressure above normal values and very high left ventricular filling pressure allowing an important preload and afterload reduction within normal limits The excessive reduction in left ventricular filling pressure may produce a decline in cardiac output according to Starling s law This occurred in one of our patients (Fig 2) Even if preload reduction is not very important it may be followed by a decline in cardiac output the optimal levels of filling pressure being 14 to mm Hg besides a small elevation of fill pressure is a compensatory mechanism in he failure

Prazosin resulted in abolition of mitral regur tation due to papillary muscle dysfunction well known effect of other vasodilators

One of the patients had pulmonary pul alternans which disappeared coinciding wi prazosin s maximum effect This may explained by a reduction in pulmona resistances and right ventricular strain

Prazosin effect is due to inhibition of t enzyme phosphodiesterase which results vascular smooth muscle relaxation and indire ly attenuates baroreceptor mediated reflexes may explain why heart rate does not increa parallel to the decline in blood pressure

II Comparison with other vasodilating agen Prazosin effect is similar to that of nitroprussi reducing both left ventricular filling pressure a aortic impedance but with a sustain effect Therefore oral prazosin offers the adva tage of both relieving pulmonary congestion as the nitrates do (they primarily redu

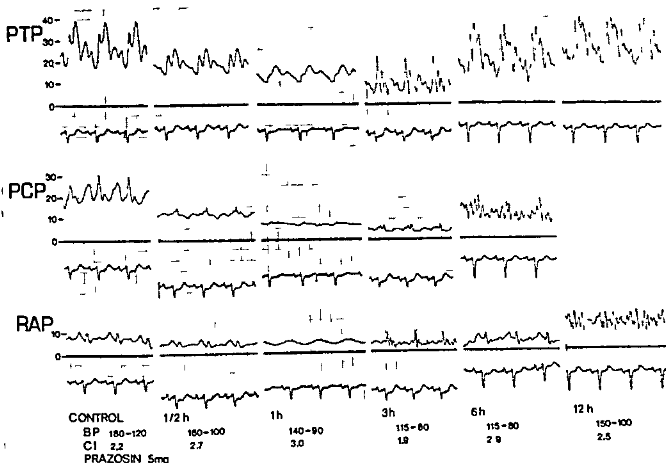


Fig 2 Changes in pulmonary trunk (*PTP*) pulmonary capillary (*PCP*) right atrial (*RAP*) and systemic blood pressures (*BP*) in mm Hg and cardiac index (*CI*) in liters/min /M after a single 5 mg oral dose of prazosin in a patient with acute myocardial infarction Note that cardiac index first increases and then decreases (after 3 hours) when left ventricular filling pressure is below optimal levels ST deviation improves 1 hour later and is depressed again 3 hours later

preload without changes in cardiac output) and increasing cardiac output by reducing afterload like hydralazine It makes oral prazosin a unique drug in the treatment of ambulatory patients with chronic congestive heart failure [1,13] However in acute myocardial infarction the drug even if effective presents three disadvantages (a) it does not have a rapid onset and the effective treatment is delayed until absortion is achieved (b) it does not have a brief duration of action so side effects like hypotension may be difficult to correct and (c) the dose depends on each patient so ventricular filling pressure may decrease to a very low level with decline in cardiac output which may be harmful extending the area of necrosis or ischemia On the other hand the dose may be too small and the optimal action is only achieved with several successive doses

Perhaps the patients from this study who passed from hemodynamic subset IV to subset II could improve even more if a greater dose were given For these reasons oral prazosin is a second choice drug in acute myocardial infarction after nitroprusside phentolamine or intravenous nitroglycerin durgs with a rapid onset of action and quickly reversible hemodynamic effects However prazosin may be a good drug after starting with nitroprusside Once the treatment has begun with intravenous nitroprusside infusion small doses of prazosin may progressively be given in order to reduce nitroprusside dose and administration time which requires exhaustive and annoying control of the patient and the dose infusion

III Myocardial oxygen supply–demand balance Evidence exists that prazosin improves the myocardial oxygen supply-demand relationship in patients with acute myocardial infarction and severe congestive failure

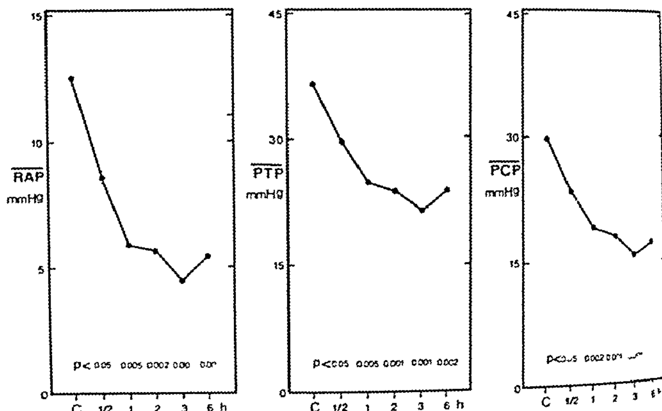


Fig 3 Modifications in mean right atrial (*RAP*) mean pulmonary trunk (*PTP*) and mean pulmonary capillary (*PCP*) pressures in mm Hg ½, 1 2, 3 and 6 hours after a single dose of oral prazosin in 11 patients with acute myocardial infarction and congestive heart failure *C* = control measurements (mean ± standard deviation)

1 Heart rate does not increase whereas the other parameters directly related to myocardial O consumption — left ventricular filling pressure systolic blood pressure and the heart rate × systolic blood pressure product—always decrease (Table I and Fig 6)

2 Prazosin has not been proved to act as an inotropic stimulating agent

3 In addition myocardial perfusion gradient values do not change and cardiac output increases both parameters probably related to coronary blood flow and oxygen supply

4 Finally coronary blood flow supply in endocardial regions with low arterial perfusion pressure may improve when end diastolic pressure decreases

In any case the danger of an excessive fall in systemic blood pressure and cardiac output especially in normotensive patients and in those with only slightly elevated left ventricular filling pressure is always present with prazosin as well as during any vasodilating therapy and may aggravate the imbalance in the myocardial oxygen supply-demand relationship by diminishing coronary perfusion pressure and blood flow This in patients with acute myocardial infarction may precipitate or augment myocardial ischemia in the peri infarction zone which could result in the extension of the infarcted area

IV Side effects Besides the transient and asymptomatic reduction of cardiac output in one patient we have not found any other side effects although severe hypotension and collapse chest pain tachycardia nausea and vomiting diarrhea and febrile polyarthritis have been reported in the treatment of hypertensive patients with prazosin

Conclusions

1 Prazosin improves left ventricular performance in patients with acute myocardial infarction and severe congestive failure By reduction left ventricular filling pressure and aortic impedance it alleviates pulmonary congestion and improves cardiac output

2 Optimal dose levels vary significantly from one patient to another

3 In acute myocardial infarction complicated

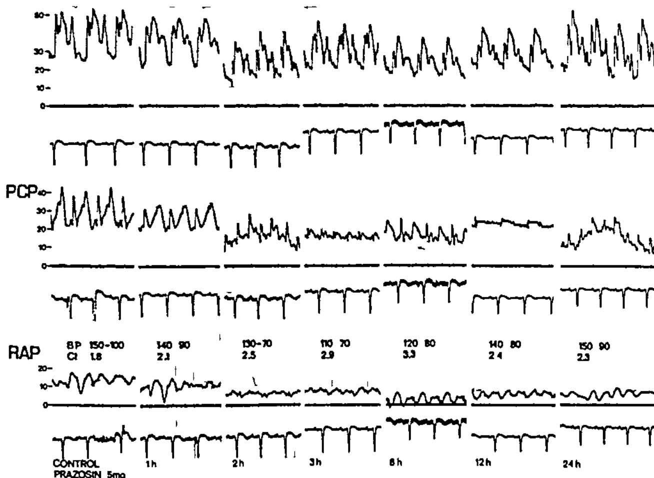


Fig 4 Sequential changes of pulmonary trunk (*PTP*) pulmonary capillary (*PCP*) right atrial (*RAP*) and blood pressures (*BP*) in mm Hg and cardiac index (*CI*) in liters/min /M in a patient with severe mitral regurgitation following acute myocardial infarction Note the disappearance of the prominent v wave 3 hours after a single dose of oral prazosin

with heart failure prazosin may improve the oxygen supply-demand balance and so reduce the area of ischemia

4 Prazosin in acute myocardial infarction can be safely used in patients with high blood pressure and severe left heart failure Hypotension is a potential hazard of the method and must be guarded against at least to the extent of not starting with a hypotensive patient

Summary

The hemodynamic effects of the new oral vasodilator prazosin were evaluated in 11 patients with congestive failure following myocardial infarction

Prazosin decreased pulmonary trunk pulmonary capillary and right atrial pressures systemic blood pressure systemic vascular and total pulmonary resistances and the heart rate × systolic blood pressure product ($P < 0.001$) Cardiac and stroke indexes increased ($P < 0.001$ and $P < 0.02$ respectively) Heart rate myocardial perfusion gradient and stroke work index remained unchanged ($P < 0.05$)

Prazosin effect began in most patients 30 minutes after an oral administration of 2.5 to 7 mg the maximum effect occurred from one to three hours later The action is sustained for at least 6 hours in most patients and sometimes is present even 12 hours after a single dose administration

We conclude that prazosin with a nitroprusside like effect improves left ventricular performance and myocardial O_2 supply-demand relationship in patients with acute myocardial infarction but optimal doses vary significantly and t'

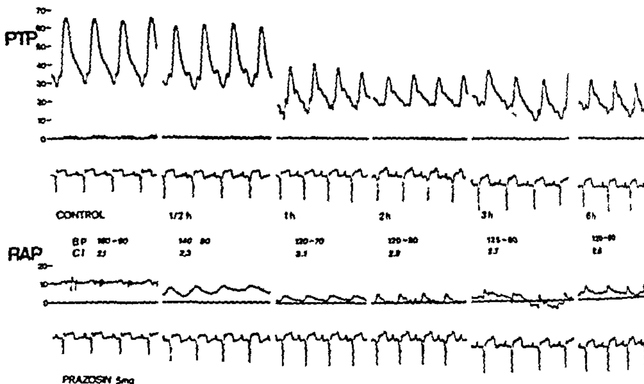


Fig 5 Typical sustained effect of oral prazosin found in most patients with acute myocardial infarction and congestive failure decline in pulmonary trunk (*PTP*) right atrial (*RAP*) and systemic blood pressures (*BP*) in mm. Hg, and enhancement of cardiac index (*CI*) in liters/min /M

Fig 6 Sequential changes in blood pressure (*BP*) in mm. Hg systemic vascular resistances (*SVR*) and total pulmonary resistances (*TPR*) in dynes/sec./cm /M ½, 1 2 3 and 6 hours after a single oral dose of prazosin in 11 patients with acute myocardial infarction and congestive failure *C* = control values (mean ± standard deviation)

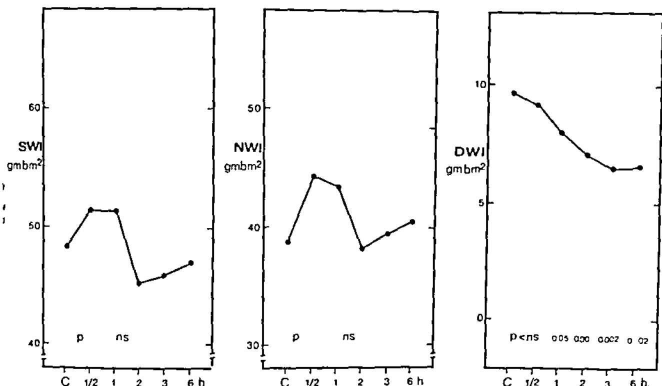


Fig 7 Chan es in left ventricular stroke (SWI) net (NWI) and diastolic (DWI) work indexes 1 2 3 and 6 hours after a single oral dose of prazosin in 11 patients with congestive failure following acute myocardial infarction (mean ± standard deviation)

hazard of severe and sustained hypotension or decline in cardiac output in patients with normal blood pressure or slightly elevated filling pressure is present

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Case reports

Echocardiography and fetal heart sounds in the diagnosis of fetal heart block

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Several cases of congenital complete heart block diagnosed antenatally by auscultation and/or by using ECG electrodes applied to the maternal abdomen or fetal scalp have been reported [2] Generally the diagnoses have been suspected when auscultation disclosed fetal bradycardia In the case reported here auscultation revealed rhythmic sounds at two distinct rates This case is remarkable because fetal atrial heart sounds were readily audible and because fetal complete heart block associated with maternal systemic lupus erythematosus (SLE) was confirmed by echocardiography *performed in utero*

Case report

A 31 year-old American Indian woman in her thirty-second week of pregnancy was hospitalized for observation after being beaten Systemic lupus erythematosus had been diagnosed three years earlier Auscultation of fetal sounds by stethoscope and using a Doptone (Smith Kline Instruments) disclosed a relatively regular heart rhythm of approximately 150 beats per minute and a regular high pitched bruit at a rate of about 40 per minute Fetal echo- and phonocardiography were performed by a method to be described and indicated atrioventricular dissociation with an atrial rate of 150 per minute and a ventricular rate of 40 per minute In the thirty fifth week of pregnancy a 2,080 gram male infant was delivered vaginally Initial postnatal examination disclosed a regular cardiac rhythm of 40 beats per minute An ECG performed after birth demonstrated complete heart block (Fig 1)

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Methods

Fetal echocardiography at 32 weeks of pregnancy was recorded with commercially available echocardiographic equipment* connected to a Honeywell 1856 Visicorder A 2.25 MHz, 7.5 cm focus transducer was applied to the mother's abdomen in the area determined by B mode scanning to overlie the fetal heart motion and many slow M mode scan nings were performed at slightly different angulations until a few satisfactory fetal echocardiograms were obtained. Fetal phonocardiography was performed immediately after the echocardiogram was obtained by amplifying the fetal heart sounds with the Doptone then placing the microphone of a phonocardiographic recorder† directly upon the Doptone s speaker Echocardiography was performed on the infant using standard technique with a 5 0 MHz near focus transducer

Results

The fetal phonocardiogram is shown in Fig 2 The ECG is that obtained from the mother The middle and lower tracings are phonocardiographic recordings demonstrating low *(LF)* and high frequency *(HF)* sounds, respectively A low pitched sound *(LPS)* followed by a high pitched bruit *(HPB)* can be seen at a rate of 39 per minute Also seen is a group of repetitive sounds *(RS)* at a rate of 150 per minute with both low and high frequency components, bearing no apparent relationship to the slower rhythm Although the sound at the slower rate may appear to be related to every other maternal QRS complex on this record a longer strip shows that they bear no constant relationship

A portion of the fetal echocardiogram with simultaneous maternal ECG is shown in Fig 3 upper panel accompanied by the infant s postnatal echocardiogram (Fig. 3 lower panel) and simultaneous ECG for comparison The latter echocardiogram is an M mode scan from the left ventricle *(LV)* inferior to the mitral valve to the aortic root *(AO)* The arrows in the postnatal recording demonstrate opening of the anterior leaflet of the mitral valve corresponding to the P waves seen in the infant s electrocardiogram [ECG (P)] The arrows in the prenatal tracing denote repetitive motions of a valvular appearing structure at a rate of 150 per minute the same as the postnatal atrial rate and the faster of the two rhythms

*Metrix Echocardiotracer
†Mingograf 34, Elema-Schonander

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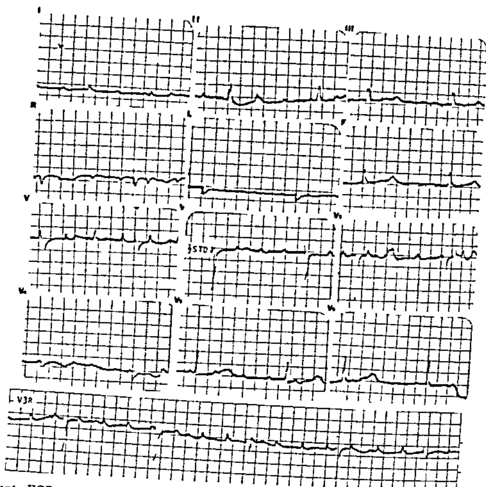


Fig 1 Infant s ECG performed shortly after birth demonstrating complete heart block with an atrial rate of 1
and a ventricular rate of 39 per minute

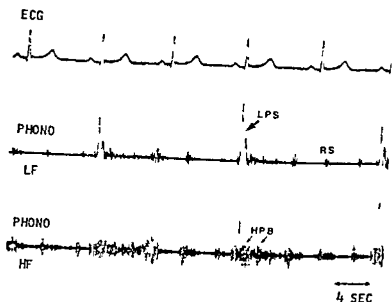


Fig 2 Fetal phonocardiogram ECG = maternal ECG LF = low frequency HF = high frequency LPS = low pitch sound HPB = high pitch bruit RS = repetitive sounds. See text for comments.

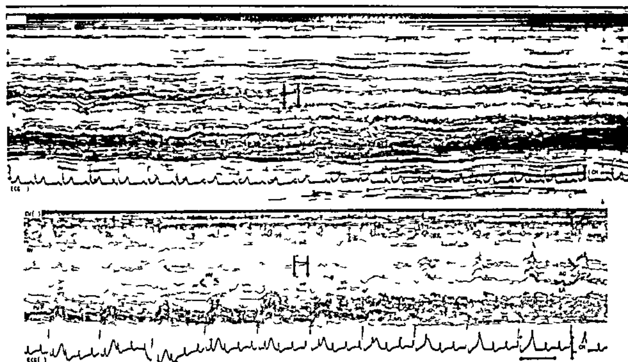


Fig 3 Patient s echocardiograms. *Upper panel* Prenatal tracing *AW(M)* = abdominal wall of mother *V* = fetal ventricle *ECG(M)* = maternal ECG *Lower panel* Postnatal tracing *CW(P)* = infant s chest wall *RV* = right ventricle *IVS* = ventricular septum *LV* = left ventricle *MV* = mitral valve *AV* = aortic valve *AO* = aortic root *LA* = left atrium *LVPW* = left ventricular posterior wall *ECG(P)* = infant s ECG Further discussion in text

heard on auscultation Fig 4 is an enlarged view of this portion for clarification

Fig 5 is an enlarged view of a portion of the right end of the fetal echocardiogram shown in Fig 3*A* This demonstrates two parallel echoes with an echo-free space posterior to them The triangular markers point to rhythmic motions of the more posterior of the parallel echoes that occur at a rate identical to those of the valvular appearing structure mentioned previously

Discussion

The use of fetal echocardiography has previously been reported in the determination of fetal heart rate as well as in attempts to study fetal heart structure and dimensions and to estimate stroke volume [4] The present study is the first report of echocardiography in the diagnosis of fetal heart block The fetal echocardiogram reported here clearly demonstrates motions of cardiac structures produced by differing independent cardiac rates Regular contractions of ventricular walls occur 39 times per minute Echoes from the valvular appearing structure within the ventricle reveal the presence of a faster rate of 150 per minute These echoes probably originate from an atrioventricular valve most likely the mitral valve They seem to demonstrate opening of the atrioventricular valve with each atrial contraction Small deflections are also present in the ventricular walls at this faster rate These findings establish the diagnosis of fetal complete heart block

An attempt to scan from mitral valve appearing structure to aortic root resulted in the appearance of parallel thin echoes which might represent anterior and posterior aortic walls with the left atrium seen posteriorly Repetitive deflections are present on the posterior aortic wall echo in both pre and postnatal echocardiograms Similar motions of the anterior wall are not seen as well Studies have shown motions of the posterior aortic wall echocardiogram to be related to left atrial volume changes thus such deflections should and do occur at the atrial rate [7]

The two rhythmic sounds heard at auscultation and recorded in Fig 2 occur at differing intervals and sound frequencies Both rhythms

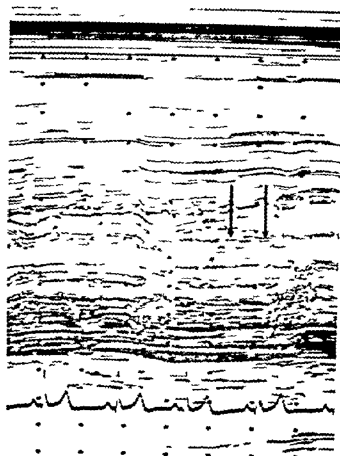


Fig 4 Enlarged view of central portion of upper panel of *Fig 3* ECG tracing *at bottom* is maternal. See text for further explanation

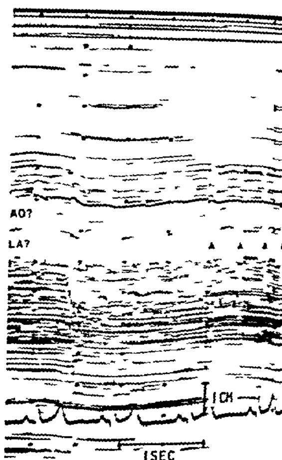


Fig 5 Enlarged view of right end of *Fig 3* upper panel. ECG is maternal. *AO?* = probable aortic root *LA?* = probable left atrium Explanation in text.

are asynchronous with the maternal ECG making it likely that both sounds originate from the fetal heart Heart sounds corresponding to atrial contraction have been reported previously in complete heart block as well as in atrial flutter and fibrillation The origins of these sounds are not entirely clear Possibilities include tensing of the atrial wall during contraction[12] downward displacement of the mitral valve apparatus associated with atrial contraction[10] vibrations of the entire cardiohemic system due to atrial contraction and the impact on the ventricular wall of blood ejected by the atrium Deflections of the atrioventricular valve the ventricular walls and the posterior aortic wall in the fetal echocardiogram are consistent with any or all of these proposed mechanisms

The mother of this infant is known to have SLE McCue and colleagues have recently reported data indicating an association between maternal connective tissue disease and congenital complete heart block The frequency with which congenital heart block occurs in the offspring of mothers having SLE is unclear this could perhaps be assessed prospectively using fetal echocardiograms Should this frequency be significant fetal echocardiography might be useful as a screening tool to detect congenital heart block in fetuses of mothers having SLE

It is possible that by chance the present echocardiogram was performed from an optimal or near optimal position Technical difficulties in recording the echo occurred because the fetus was continually in motion Further work is needed to determine the feasibility of routinely obtaining useful fetal echocardiograms and to develop methods for achieving good quality recordings. Echocardiographic techniques might then be useful in detecting other fetal cardiac defects and in studying fetal cardiac physiology

Summary

A 32 week fetus was demonstrated phonocardiographically and echocardiographically to have

a regular atrial rate of 150 per minute and a regular ventricular rate of 39 per minute indicating complete heart block The diagnosis was suspected when two groups of heart sounds at two distinct rates were heard on auscultation and was confirmed by the postnatal ECG The maternal history was significant for the presence of systemic lupus erythematosus The basis for the echocardiographic diagnosis of complete heart block the presence of atrial heart sounds in complete heart block and the relationship of maternal SLE to congenital heart block are discussed

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Pregnancy in a patient with porcine valve xenografts

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In recent years advanced surgical techniques and improved prostheses have afforded valve replacement to a larger and younger patient population A subgroup of this population women of child bearing age presents particular problems The management of pregnancy in women with mechanical valve prostheses is extensively reviewed[1-8] with major complications being thromboembolism and endocarditis Anticoagulation advocated to prevent thrombosis and embolism is problematical because of medication related teratogenic and hemorrhagic effects The use of valves that do not require anticoagulants should reduce these complications[4, 9] Porcine xenografts appear to obviate the need for anticoagulants except in specific instances[10] but experience in pregnant women is limited

Presented is a case of a young woman with porcine xenograft aortic and mitral valves and her management through pregnancy

Case report

The patient is a 23 year-old white female who had rheumatic fever at age 12 and a recurrence at age 16 She had an uncomplicated pregnancy at age 21 (1976) with a spontaneous vaginal delivery of a normal infant Postpartum her cardiac status deteriorated with recurrent atrial fibrillation heart failure and pulmonary edema despite aggressive medical management

Cardiac catheterization several months after delivery (July 1976) demonstrated severe mitral regurgitation aortic regurgitation and increased pulmonary vascular resistance (Ta I) In October 1976 he had replacement of both aortic mitral valves with porcine prosthesis 23 mm and 29 m respectively Postoperatively her cardiac function markedly improved Oral anticoagulants were discontin three months after valve replacement

The patient remained in good health and became preg with an expected date of confinement in March, 1978 In first trimester she gained approximately 30 pounds (heigh ft. 2 in weight 210 lbs) and reported mild fatigue exertional dyspnea At 22 weeks gestation she was re ent the University of Minnesota Hospitals Evaluation sh absence of congestive heart failure or arrhythmia She continued on digoxin (0 25 mg daily) and furosemide (40 daily) with potassium supplementation and prenatal v mins A balanced diet emphasizing both sodium restric and weight control was prescribed. She was also encour to take frequent left lateral recumbent rest periods during day and to wear pressure-graded elastic stockings at n h

During the subsequent 18 weeks she gained an addition pounds despite weekly nutritional counseling without cha in symptoms or signs of cardiac deterioration. Electrocar grams demonstrated occasional premature atrial contracti Serial echocardiograms revealed left atrial and ventric chamber enlargement with normal motion of th prosth valves. The echocardiograms were unchanged from those p to pregnancy Tests of clotting function including plate prothrombin time partial thromboplastin time and thro time were all within normal limits

On March 13 1978 spontaneous rupture of membr occurred and the patient was admitted to the obstetric u Subacute bacterial endocarditis prophylaxis was immedia begun with intravenous vancomycin (500 mg every 6 ho and was continued for the ensuing three days. There w history of penicillin allergy Dysfunctional labor necessit intravenous oxytocic augmentation A central venous p sure line was inserted and showed normal pressures thro out labor Regional anesthesia midforceps rotation extraction were used for vaginal delivery of a 3 4?0 gram infant with APGAR scores of 8 9 and 9 at 1 ? and 5 minu respectively The estimated blood loss was 300 c.c and patient left the delivery room in satisfactory condition. The patient s immediate postpartum c urse was cor

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cated only by a persistent upper respiratory infection There were no symptoms or signs of congestive heart failure arrhythmia or embolization Routine laboratory data elec trocardiograms, chest x rays, and an echocardiogram were unchanged She was discharged home on the fifth postpartum day She and the infant remained well four months after leaving the hospital.

Discussion

The clinical course of pregnancy in a young female with aortic and mitral porcine valves presents several management problems

Pregnancy results in a hypercoagulable state due to increases in specific clotting factors plate let adhesiveness and plasma fibrinogen[11, 1] When combined with circulatory stasis due to anatomical changes there exists a setting condu cive to thromboembolism[13] Thrombosis and embolism are also major threats following replacement of mechanical cardiac valves[14] Attempts to reduce that risk include anticoagu lants agents reducing platelet adhesiveness and development of non thrombogenic material for valve structures and coverings There is consider able literature describing management of preg nancy in patients with mechanical valves[1] The need for anticoagulation is particularly proble matic because of teratogenicity and peripartum hemorrhagic complications[2, 3, 5] Despite these dangers the threat of thromboembolism is suffi cient with most prosthetic valves that some method of anticoagulation is recommended and widely used It is clear that a valve prosthesis that does not necessitate the administration of anticoagulants would be preferable

In a comparison study of the Starr Edwards caged ball valve and the Hancock porcine pros thesis Oyer and associates reported that the porcine valve significantly reduces the incidence of thromboembolic and hemorrhagic complica tions without increased rates of valve failure or endocarditis Other reports also describe very low incidence of thromboembolism in recipients of a single porcine mitral valve (0 to 5 per cent) over 2 to 5 year follow up periods Long term anticoagulation was not routinely prescribed in any of these patient groups with the majority of reported complications occurring during the first three postoperative months Thus for porcine valves several authors recommend anticoagula tion for the initial three postoperative months followed by tapering and discontinuation unless intercurrent thromboembolism has occurred or the patient shows left atrial enlargement or atrial fibrillation[1, 20]

Table I Catheterization data

	Pressures	
	Rest	*Exercise*
LV (mm. Hg)		
Phasic	124 / −7 19	140 / 0 30
Pulm art (mm Hg)	64 / 30 41	85 / 43 67
Cardiac output (liters/min)		
Fick	2.8	4.2
Thermo dilation	3 0	4 3
Systemic resistance (DSC)	2,734	2,171
Pulm art resistance (DSC)	436	85[illegible]

Abbreviations DSC = Dyne second per centim ter LV = left ventricle mm Hg = millimeters of mercury Pulm art = pulmonary artery

The experience presented in this case report supports the observations that routine anticoagu lation is not necessary with porcine valves even during the hypercoagulable state of an uncompli cated pregnancy However atrial fibrillation left atrial thrombus or other thrombogenic condi tions were not present and may indicate the need for anticoagulation even with xenografts

As with all cardiac patients close monitoring of cardiac status during pregnancy delivery and postpartum is necessary

Summary

The course of pregnancy and successful vaginal delivery of a healthy infant in a 23 year old woman with previous aortic and mitral valve replacement with porcine xenografts is presented Unlike the management of pregnant patients with conventional mechanical prostheses anti coagulation may not be necessary with xeno grafts particularly when there are no other thrombogenic conditions Other management issues include congestive heart failure arrhyth mias prophylaxis against subacute bacterial endocarditis and expeditious labor and delivery

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Clinical pathologic conference

The consequences of the inconsequential Marantic (nonbacterial thrombotic) endocarditis

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J. Keith Campbell, M.D.
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Case presentation

Dr. Olney: Mrs. B. L., a 47-year-old hairdresser and housewife, was admitted to the Rochester Methodist Hospital on September 6, 1977. She had enjoyed good health until mid-July, 1977, when she experienced transient swelling of the right arm. This resolved spontaneously, but in early August she noted progressive malaise, anorexia, cough, fatigue, and weight loss. A chest x-ray on August 16, 1977, demonstrated a right hilar shadow and she was treated initially with antibiotics but failed to improve. On August 29, 1977, a right supraclavicular lymph node biopsy was performed and the diagnosis of metastatic anaplastic carcinoma of the lung was made.

Subsequent questioning brought forth the fact that between June, 1977, and September, 1977, she had suffered five separate episodes of blurring of the right field of vision, lasting up to 15 minutes and on one occasion associated with vertigo. During the five days prior to her coming to Rochester, she developed dysarthria and a left hemiparesis progressing from the onset to peak in approximately 36 hours.

Physical examination at the time of her admission to Rochester Methodist Hospital on September 6, 1977, demonstrated normal vital signs and a normal cardiovascular examination. Right supraclavicular nodes were present. She was dysarthric with flaccid paralysis of the left arm and weakness of the left leg. Babinski, Chaddock, and Oppenheim reflexes were present on the left, and the left deep tendon reflexes were diminished in comparison with the right.

Laboratory assessment included a white blood count of 27,900 per mm^3 with 93 per cent neutrophils. The hemoglobin was 13 gm. per cent and the platelet count was 239,000 per mm^3. The serum creatinine, bilirubin, alkaline phosphatase, SGOT, total protein, calcium, phosphorus, sodium, potassium, uric acid, and fasting blood sugar were all normal. A right hilar mass was present on chest x-ray with an extensive perihilar infiltrate in the right middle and upper lobes (Fig. 1). The electrocardiogram was normal.

A computerized tomography (CT) brain scan with contrast injection showed homogenous enhancement low in the right frontal lobe extending deep toward the basal ganglion (Fig. 2). This finding was felt to be compatible with an isodense infarct. A dynamic brain scan showed a decreased flow in the right middle cerebral artery distribution with an increased uptake in the right fronto-parietal region. These findings again were considered most consistent with an infarct.

By the time of her hospital admission the patient was already aware of some improvement in her neurologic status over the preceding 24 hours. She was begun on prednisone at 60 mg. daily along with a program of physical therapy and showed continued improvement over the course of the hospitalization. She was dismissed on September 17, 1977, on a tapering dose of prednisone and a home program of physical therapy. Her improvement continued until Septem-

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Fig 1 Chest x ray taken on the initial admission on September 6 1977 with findings of a right hilar mass and perihilar infiltrate involving the right middle and upper lobes

ber 22 1977 when she developed sudden weakness and fell to the floor with a complete paralysis of her left side This persisted and she returned to be readmitted to the Rochester Methodist Hospital on September 26 1977 Examination confirmed the presence of a complete left hemiplegia

A repeat CT scan showed an increase in the size of the previously noted lesion An additional 'new lesion was evident in the right frontal parasagittal region (Fig 3) The official interpreter noted that because of the multiplicity of lesions now and the progression of the original lesion I would think that logic would dictate that these are metastatic in nature rather than infarct

A course of radiotherapy was begun anticipating 3000 rads to the head over a period of two weeks Despite this she failed to improve and by the eleventh day it was evident that she was getting progressively worse with increasing lethargy and difficulty in swallowing On October 10 1977 profound acrocyanosis was noted associated with tachypnea tachycardia and deteriorating sensorium and she died that evening

Clinical discussion

DR SCHATTENBERG The bare essential facts of this lady s case would seem to be that she had a four month illness characterized by the presence of a lung mass and a progressive downhill course central to which were the recurrent neurologic lesions We know from the protocol that she had an undifferentiated carcinoma of the lung but even though this is a cardiovascular CPC all who examined her described a completely normal cardiovascular examination

The admission chest x ray did indeed show hilar adenopathy and a picture consistent with an obstructive pneumonitis or fluid in the interlobar fissure The cardiac silhouette appears completely normal (Fig 1) Since her clinical history smacks of cerebral embolic disease one must raise the question of an intracardiac shunt with paradoxical emboli With this normal cardiac silhouette no previous cardiovascular history and normal auscultation by several good observers I find it most unlikely that she could have something of that order In addition the ECG was normal

Next let us consider the CT scans Dr Campbell is here to help us out at this point

DR CAMPBELL On the initial study of September 9 1977 (Fig 2) the striking finding is an area of enhancement following injection of iodinated contrast medium There is no surrounding abnormality and on the noncontrast CT scan we see nothing at all This then is an isodense lesion, that is one which has the same density as normal brain tissue but which does take up the contrast dye This finding unfortunately is rather nonspecific The radiologists tend to think of an isodense lesion as being most likely an infarct but it could be a glioma an abscess a metastasis or virtually anything and one must know more about the patient to arrive at a more specific diagnosis The other thing to mention is that there is no mass effect The ventricle if anything is a bit bigger on the affected side Therefore, it is not being compressed or shifted

DR SCHATTENBERG She was treated with prednisone and seemed to show some improvement by the time of dismissal I would not place much importance on the fact that she improved with prednisone as any type of inflammatory process or even embolic event could show modest improvement on steroids

She was dismissed initially on September 1[illegible]

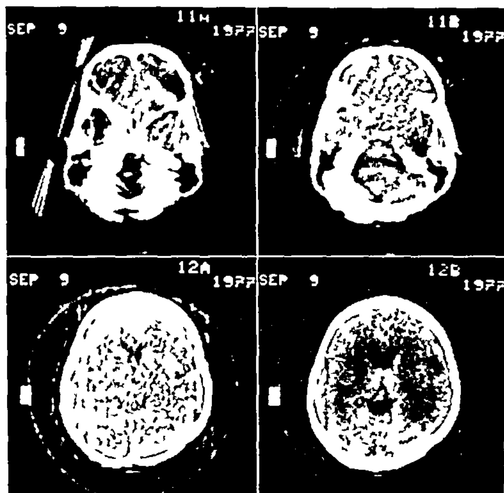


Fig 2 CT (computerized tomography) scan of the head done on September 9 1977 following contrast injection. The series (frames 11A 11B 12A and 12B) shows enhancement extending from near the base of the skull up to a plane below the right frontal lobe

1977 on a tapering schedule of steroids and a home program of physical therapy At first she did well but then five days later she collapsed this time with a complete left sided paralysis The affected area is the same so presumably this new process has struck the same area of the brain as before From animal studies we know that embolized glass beads have a peculiar propensity to direct themselves along basically the same vascular route each time so that her recurrent right sided lesions would be consistent with emboli She was rehospitalized on September 26th and another CT (Fig 3) scan was performed The contrast study was of limited quality due to patient motion so we have only the noncontrast study

Dr Campbell In this instance there is an area which is less dense than the corresponding area on the other side and it seems to be connected to the ventricular system As one examines several slices it would appear probably to follow an anterior cerebral artery distribution

Dr Schattenberg We are still left at least from a neurologic standpoint with a differential between embolic disease and metastatic disease Since this is a cardiovascular CPC I am inclined to believe that it is embolic It is time therefore to consider the differential diagnosis of emboli originating from the heart Mural thrombus probably accounts for the largest number of cardiac emboli However with a completely normal clinical examination a completely normal cardiac silhouette and a completely normal electrocardiogram it is, to my mind impossible for her to have had a myocardial infarction or cardiomyopathy or any other likely cause for a mural thrombus leading to this series of embolic events. I

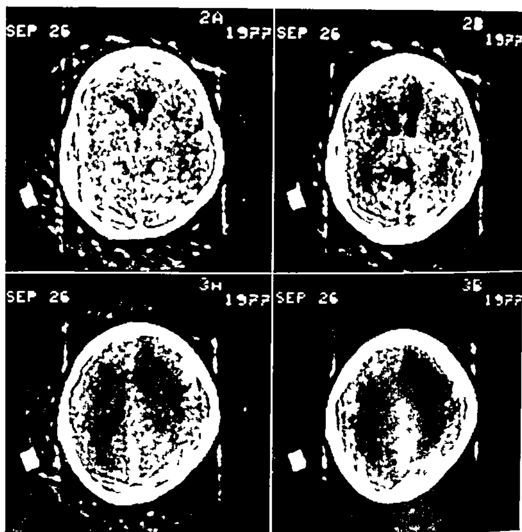


Fig 3 CT scan of the head done on September 26 1977 *(frames 2A 2B 3A and 3B)* during the patient s second hospitalization showing a large area of relative decrease in density involving the right frontal lobe

would have to say the same regarding a possibility such as left atrial myxoma These possibilities could have been satisfactorily excluded by a negative M mode or sector echocardiographic study

You will recall that her white blood cell count was 28 000 per mm ³ when she came in but she was afebrile It is still conceivable that she could have bacterial endocarditis One would be postulating septic emboli however and it would be most extraordinary for a case of bacterial endocarditis with emboli not to proceed along a more hectic course with abscess formation fever and a more typical septic toxic picture Terminally she did develop a temperature of 102 F but this seemed likely a manifestation of her generalized debili tated state

In sum therefore I do not think that mural thrombus or left atrial myxoma are reasonable possibilities and I do not think bacterial endocarditis is a good diagnosis either Earlier I rejected the idea of intracardiac shunt with paradoxical emboli

I am left finally with a diagnosis which has been known by a variety of names the most popular name being marantic carditis or nonbacterial thrombotic endocarditis (NBTE) This entity is mostly found in patients with chronic debilitating diseases and carcinomatosis is by far the commonest cause My diagnosis is therefore *NBTE associated with carcinoma of the lung with systemic embolization to the right cerebral hemisphere*

Dr Milton W Anderson Would you consider the possibility that her undifferentiated lung carcinoma had involved the pulmonary veins or

the left atrium and perhaps the emboli are actually cancer emboli?

DR SCHATTENBERG Yes I think that could be another possibility

DR CAMPBELL I will run through some of my own thoughts regarding this case but first let me make a couple of comments about the radiologist s report of the CT scan When radiologists interpret findings that are relatively nonspecific or that may be associated with many conditions they will often offer diagnoses which conform to the patient s clinical history or to the clinician s presumptive diagnoses In other words the decrease in density in CT scans is not specific nor is the finding of a mass effect with shift of the ventricular system specific Twenty five per cent of cerebral infarcts will show a large mass effect which can occur within 24 hours of the infarct and can last for as long as 28 days Obviously if you have two or more CT scans and the shift is getting progressively worse then this is likely to be a glioma or at least a neoplasm rather than an infarct

The dye enhancement in CT is also nonspecific We have now shown that virtually anything which breaks the blood-brain barrier will take up the dye though some things do so more than others In our experience at least 5 per cent of infarcts will show enhancement Others have claimed that at least 50 per cent of infarcts will enhance Abscesses will show a big ring of enhancement but an area of encephalitis before it becomes an abscess will also show enhancement We are beginning to realize more and more that the CT scan is like the brain scan You can see an area of decreased or increased attenuation but it does not by virtue of its density give you a specific diagnosis Its shape or its position might

Let me turn now to run through some of my thoughts on this lady s illness There seemed to be a lot of things going on in her right side Firstly she had a swelling of the right arm which we have not explained Then she developed right supraclavicular nodes and I should think it possible that they caused a venous occlusion to account for the swelling She also had these episodes of blurring in the right field of vision The meaning of that is always hard to be sure about even when you have the patient right in front of you If they mean the right field then one has to think of a left hemisphere lesion but if by the right field they mean what they can see out of their right eye then one must obviously think of the right carotid circulation I would like to think that she was having difficulty in seeing out of the right eye but that is only so that I can fit it in with my theory

If it were the case that she indeed had a true right field defect then something must have happened to her left cerebral hemisphere and with subsequent events that would imply an embolus from a very proximal source either the aorta or the heart

If on the other hand she were simply having difficulty seeing out of the right eye this would work better with my notion of the subsequent events involving her left limbs and right hemisphere lesions I could return to the right supraclavicular lymph nodes again and say that while it is very rare it is nonetheless possible to have a tumor invade the carotid artery and produce emboli of either tumor or clots that form over the break in the intima The end result would be emboli from a local lesion in the right carotid with the distribution of defects along its course

Another bit of evidence to support the diagnosis of emboli comes from the isotope brain scan which was reported as showing a decreased flow in the right middle cerebral artery territory followed by an increased uptake in the right anterior fronto parietal region on the static film That would suggest that she had at least two arteries occluded and support the likelihood of emboli be it from the heart as Dr Schattenberg has suggested or as I have suggested from the carotid artery

As her course progressed she developed difficulty in swallowing I am assuming this was just an apraxia of swallowing associated with her major illness and secondary to the frontal lobe infarct If it represented trouble with her tongue of a lower motor neuron type that would imply a posterior fossa lesion and I would be hard pressed to fit that in with her other neurological findings

In summary then I would think that these lesions in her head were caused by emboli rather than metastases Instead of putting the source in the heart I would wonder whether the emboli were coming from the carotid I would certainly not discount the theory though that these were emboli coming from the heart associated with marantic endocarditis

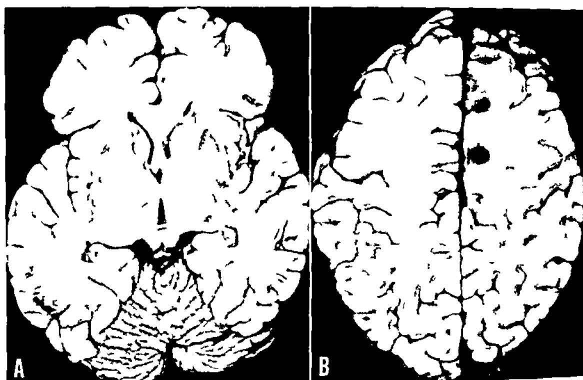


Fig 4 A and B Gross appearance of the brain as sectioned along the planes of CT scan *A* corresponds to *frame 12A of Fig 2* and *frame 2A of Fig 3* and *B* corresponds to the *plane between frames 3A and 3B of Fig 3*

Dr Schattenberg s clinical diagnoses

1 Undifferentiated carcinoma of the lung

2 Nonbacterial thrombotic (marantic) endocarditis with emboli to the right carotid circulation resulting in right cerebral hemisphere infarcts

Dr Campbell s clinical diagnoses

1 Undifferentated carcinoma of the lung

2 Local invasion of the right carotid artery with resultant emboli (tumor and/or thrombus) and right cerebral hemisphere infarcts

DR OLNEY We will now ask Dr Okazaki and Dr Lie to tell us what were actually found at autopsy

Pathologic discussion

DR OKAZAKI I will describe only the autopsy findings of the central nervous system of this patient and leave Dr Lie to give the other findings and his concluding comments

The brain was fixed in formalin and was dissected later along the planes of CT scan images Corresponding to the areas of enhanced attenuation after contrast media injection noted in the CT scan of September 9 1977 (Fig 2) there was an area of old predominantly cortical infa[rc]tion involving the right inferior frontal gyrus a[nd] insula (Fig 4A) This also correlated well with t[he] findings of dynamic brain scan The cingula[te] gyrus and the right half of the genu of the corp[us] callosum on the same plane showed more rece[nt] softening

In more dorsal slices such as shown in Fig 4[B] this recent infarction extended into the med[ial] aspect of the right superior frontal gyrus wh[ich] was slightly hemorrhagic in the cortex Mo[re] lateral and dorsal to and contiguous with th[is] area the right superior and middle frontal g[yri] were involved in non hemorrhagic forms of rece[nt] infarction Together they corresponded to t[he] right frontal areas of decreased attenuation not[ed] in the CT scan on September 26 1977 Al[so] present in the more distal areas of the ri[ght] middle cerebral artery distribution were multip[le] smaller areas of cortical rarely subcortic[al] infarction of an age comparable to that of th[e] larger right inferior frontal insular infarct A fe[w] more minute ones were found in the right post[e]rior cerebral artery distribution as well The[y] were visible in the slice shown in Fig 4B The[re] were multiple minute cortical infarcts both o[ld] and recent in the cerebellar hemispheres



Fig 5 A, B and C Histologic appearances of emboli of different ages in leptomeningeal arteries. A a recent embolus resembling closely the appearance of the vegetation found on the aortic valve B an "older" embolus in a more advanced stage of organization and C a completely organized embolus with small recanalized channels. The underlying cortex shows old cystic infarction (Hematoxylin and eosin stain original magnification ×160)

Microscopically numerous thrombi in different stages of organization were seen in the leptomeningeal arteries corresponding to the areas of infarction noted grossly Their histologic appearances were demonstrated in Fig 5A B and C and were compatible with their embolic genesis from nonbacterial thrombotic endocarditis of the aortic valve The occluded vessels were virtually free of atherosclerosis and showed no other preexisting mural abnormalities

The larger emboli such as those found in the proximal right anterior cerebral artery and the trifurcation of the right middle cerebral artery were easily detected grossly and were of recent origin resembling histologically that demonstrated in Fig 5A The presence of similar emboli in the proximal and multiple distal branches of both the anterior cerebral and middle cerebral arteries may be explained as being roughly simultaneous in lodging or as due to fragmentation and distal migration of a more proximal and larger embolus There was no evidence of metastatic neoplasm either in the cerebral vasculature or in the brain parenchyma

Dr Lie A large partly necrotic squamous cell carcinoma was found at autopsy occupying a major portion of the right lung Metastases were present in the left lung hilar lymph nodes right hemidiaphragm pericardium and epicardial blood vessels and lymphatics. The source of cerebral emboli was indeed in the heart The heart was somewhat heavier than expected (368 Gm.) but showed only minimal coronary atherosclerosis Large multiverrucal type thrombotic vegetations were present on the posterior (noncoronary) and right anterior aortic valve cusps The aortic valve cusps were structurally intact otherwise and showed no inflammatory process The verrucous vegetations consisted of bland thrombotic material only and no microorganisms were identified Other cardiac valves were free of disease The vegetations on the right anterior aortic valve cusp were so well positioned and at such proximity to the right coronary ostium (Fig 6A) that one would be extremely surprised not to find evidence of embolic occlusion somewhere in the distribution of the right coronary artery We had such evidence Multiple small discrete recent infarcts were found in the posterior (inferior) wall of the left ventricle (Fig 6B) Recent infarcts were also

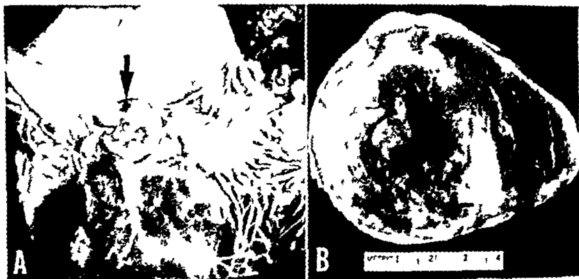


Fig 6 A and B Gross appearance of the heart A opened aortic valve showing large verrucous vegetations on the posterior and right anterior aortic valve cusps directly opposite the ostium of the right coronary artery (arrow) B a transverse slice of the heart showing nontransmural infarcts in the posterior wall of the left ventricle (arrows)

found in the spleen and kidneys Numerous thrombotic emboli of different histologic ages (recent and old) were present in the microvasculature of the heart (Fig 7) the spleen and kidneys In addition tumor emboli were found quite extensively in the epicardial lymphatics (Fig 8) and occasionally in intramyocardial vessels The carotid arteries did not have occlusive lesions Thus although carcinoma of the lung was the apparent major clinical problem death in this patient was the direct result of widespread cerebral and cardiac emboli from NBTE of the aortic valve

In summary the *anatomic diagnoses* were (1) squamous cell carcinoma of lung with widespread thoracic metastases including epicardial lymphatics (2) nonbacterial thrombotic endocarditis of aortic valve with recent and old thrombotic emboli in the brain heart spleen and kidneys (3) recent and old infarcts in the right cerebral hemisphere and (4) recent nontransmural myocardial infarction splenic infarction and renal infarction

General comment

A number of recent papers have emphasized the main clinical and pathologic features of nonbacterial thrombotic endocarditis (NBTE)[1] Although NBTE is seldom diagnosed clinically it can no longer be regarded as the older terminology had implied (by names such as marantic terminal, or cachectic endocarditis endocarditis simplex or endocarditis minima and degenerative verrucal endocardiosis) as a harmless or inconsequential incidental autopsy finding in the ol… terminally ill or wasted patients The incidence of NBTE is most probably on the rise, and ha… been so for some time [illegible] In a recently published review Deppisch and Fayem found 65 documented cases of NBTE in 4 096 autopsies (1 6 per cent) This is a significantly higher incidence than that documented in an earlier report by Barron and associates[2] who could find only … cases in 18 486 consecutive autopsies. Reagan and Okazaki[3] found 74 cases in a 10 year survey at the Mayo Clinic Contrary to earlier reports, the incidence of peripheral embolization is quite high[3,4] Cerebral emboli with infarction have been present in over 50 per cent of cases in recent reports Embolic splenic and renal infarcts are also common Less common but potentially serious are the coronary emboli with documented cases of resultant myocardial infarction.[4] Examples of emboli to virtually all major arterial systems and organs have been reported and in a significant number of cases have been the event responsible for the patient s demise

A further point of interest is the small number of cases where embolization from marantic endocarditis is the first manifestation of underlying malignancy [illegible] In a number of such cases [illegible] sies demonstrated that the underlying maligna…

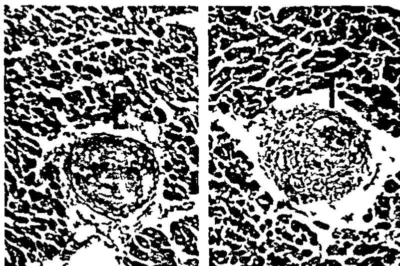


Fig 7 Photomicrographs showing a recent thrombotic embolus *(E)* and an organized tumor embolus *(T)* in the intramural small vessels of the heart (Hematoxylin and eosin stain original magnification ×240)

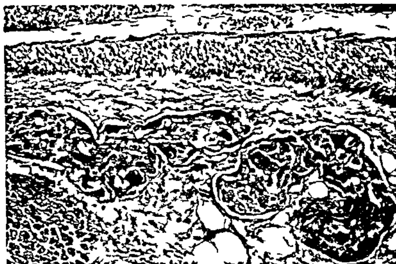


Fig 8 Photomicrograph showing metastatic squamous cell carcinoma of the lung in epicardial lymphatics (Hematoxylin and eosin stain original magnification ×240)

cy was still localized and potentially resectable

The clinical diagnosis of NBTE has rarely been made in the past due in part no doubt to a lack of awareness but also due to its virtual silence Murmurs are the exception rather than the rule regardless of which valves are affected Likewise since this form of endocarditis causes little or no hemodynamic derangement there have been no easy diagnostic techniques for establishing its presence ante mortem However with recent advances in echocardiography especially the sector scanner the demonstration of valvular vegetations has been significantly improved The opportunity for ante mortem diagnosis of NBTE will likely be enhanced by this technique as well It is important therefore to maintain a clinical suspicion and recognize the clues to the presence of NBTE

It is generally believed that NBTE is a manifestation of disseminated intravascular coagulopathy (DIC)[3,7] Another common manifestation of this process is thrombophlebitis Thus the

combination of phlebitis with peripheral arterial emboli without otherwise obvious source is considered a clue to the possible presence of NBTE. Other subtle evidences of DIC such as elevated prothrombin time, slightly low platelet count, or increased fibrin split products are worth seeking in this setting, and of course if a malignancy is not already known to be present it should also be sought.

Theoretically, a DIC syndrome should improve with antithrombotic therapy, and some have suggested this approach with NBTE. The thrombotic manifestations of malignancy, unfortunately, have always been notoriously resistant to anticoagulant treatment, and while there has been little or no reported experience with the treatment of NBTE with anticoagulation or antiplatelet agents, it seems unlikely that this mode of treatment would effect significant change in its clinical course.

Ideally, one would have liked to deal with an early, non metastasizing and resectable carcinoma, the removal of which might eliminate the entire problem. Realistically, however, that would be the rare exception. Most often NBTE occurs in the setting of an altogether too well known malignancy which is already widely metastatic and beyond cure. Be that as it may, in many instances the ante mortem diagnosis of NBTE need not serve only to give intellectual satisfaction to the physician. The consequences of this manifestation, at one time thought to be an inconsequential entity, can be instantly devastating to some patients and can contribute adversely in the long run to the morbidity and mortality of most other patients. The recognition of its presence may add measureably to the quality or logic of clinical decisions in the management of these patients.

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Treatment of acute glomerular nephritis

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Acute salt and water retention when associated with a rapid rise in blood pressure and a sudden deterioration of renal function form the main features of an acute nephritic syndrome It may be preceded by an infection by the streptococcus pneumococcus meningococcus mycoplasma the Epstein Barr virus mumps etc or may be a manifestation of a systemic disease such as systemic lupus erythematosus polyarteritis no dosa or the Henoch Schonlein syndrome When it is associated with an infection it is customary to use the term acute glomerular nephritis and include when it is known the name of the causative organism—e g acute streptococcal glo merular nephritis Whatever its etiology the treatment of an acute nephritic syndrome has many points in common The treatment of acute streptococcal glomerular nephritis will be consid ered here It can be divided into prophylaxis prevention of death during the acute phase and therapeutic attempts to influence the eventual course of the disease

Acute streptococcal glomerular nephritis can occur in epidemics due to a specific strain of nephritogenic streptococcus The prompt and widespread administration of an injection of long acting penicillin to all who have had close contact with a case of streptococcal acute glomerular nephritis will therefore effectively suppress an epidemic It is questionable whether such persons having had close contact should have their throats cultured before treatment so as to identi fy those individuals who are infected Unless there is a history of penicillin sensitivity it is probably better to anticipate this procedure Awaiting the result of bacteriological screening can be performed on those subjects who are less likely to be infected It is not so certain whether penicillin if administered after an overt active streptococcal infection can influence the even tual course of events But it is nevertheless important to give antibiotics for some time after such an infection Its main purpose then is to shorten the period of infection and to prevent a re infection which can either prolong or cause a recrudescence of the clinical features of the disease

During the acute phase though the heart s functional capacity as a pump is normal the increase in intrathoracic blood volume may give rise to acute pulmonary edema or the blood pressure may oscillate with such devastating effect as to cause hypertensive encephalopathic fits or acute renal failure may occur These rare acute complications may cause death in about 1 per cent of persons with overt acute glomerular nephritis

Most patients with acute glomerular nephritis are breathless particularly children Acute pulmonary edema sometimes develops when the patient is admitted to hospital and put into bed At home if his breathlessness is troublesome the patient has probably had the intuitive good sense to stay upright in an armchair If breathlessness is pronounced therefore it is better during the first 24 hours to have the patient in a comfortable armchair than in bed If this is insufficient to control the breathlessness then it is necessary to give morphine and to perform a venesection of up to 500 ml This is quicker and more effective than rotating tourniquets and certainly more com fortable for the patient than positive pressure respiration both of which are alternative treat

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ments As there is *nothing the matter* with the heart the heart rate is usually regular and as there is usually some renal functional impairment it is not only unnecessary but dangerous to give digitalis Lowering the blood pressure however may be of help in controlling the pulmonary edema But it is more important to ensure that there shall be no further retention of salt and water and occasionally to try and get rid of some of the retained fluid If breathlessness is not prominent, the salt and water retention is most easily treated by withholding salt and water It is a useful rule to withhold all fluids and food by mouth for the first 24 hours At the end of that time there is bound to be some loss of weight and the pattern of urine flow will have become evident Further instruction can then be given accordingly If there has been a brisk diuresis of over a liter of urine in 24 hours and renal function has not deteriorated further the patient can be allowed an intake of 1 500 ml of fluid 50 mEq of sodium chloride, and a normal protein intake If on the other hand there has been a smaller 24 hour output of urine then the intake of fluid for the next 24 hours should be restricted to 400 ml plus an amount equivalent to the volume passed as urine during the preceding 24 hours The 24 hour sodium intake should also be lowered to 10 mEq and the protein intake to 0 5 g/kg The administration of furosemide in acute glomerular nephritis is stated to be effective and innocuous Nevertheless this agent is not always effective and it is theoretically repellent to subject an acutely diseased kidney to a tubular poison If there is an overwhelming necessity to remove salt and water rapidly and venesection is contraindicated or needs supplementing this can be achieved by the oral administration of 70 per cent sorbitol until the onset of diarrhea In this way it is possible to cause a reduction in the patient s weight of 3 to 5 kilograms in a few hours and simultaneously to relieve the often present hyperkalemia Alternatively peritoneal dialysis or hemodialysis may be used The use of sorbitol is simple painless can be performed in any setting and in contrast to the two alternatives is almost free from complications

These various maneuvers to try and control the retention of salt and water are also relevant for the treatment of hypertensive encephalopathy for the blood pressure will tend to settle as the patient unloads his edematous fluid Usually the hypertension needs no specific treatment, but if its height causes concern or hypertensive encephalopathy has occurred the blood pressure should be lowered with a suitable rapidly acting hypotensive agent such as hydralazine bethanidine, diazoxide or minoxidil. If the hypertensive encephalopathic attacks do not cease immediately the quickest way to suppress them is to anesthetize the patient with an intravenous barbiturate agent such as thiopental sodium which also lowers the blood pressure Subsequently the patient will only slowly regain consciousness during which time the blood pressure can easily be controlled by other means.

It is not usual for the degree of renal failure to need specific treatment, except possibly for some initial restriction of protein intake Occasionally however the blood urea and plasma creatinine continue to rise, the oliguria persists, and it becomes increasingly difficult to control the hypertension and salt and water retention All three can be effectively managed with hemodialysis It is important that this should be started before the blood urea reaches 200 mg /100 ml and that it should be repeated at frequent intervals preferably daily until recovery In children renal function is likely to return to normal. Adults are less likely to recover and may have to continue on maintenance hemodialysis indefinitely

The usual patient with acute glomerular nephritis has none of these severe complications Diuresis and natriuresis occur within a day or two of admission to hospital The clinical evidence of salt and water retention disappears the blood pressure returns to normal and renal function improves But microscopic hematuria and proteinuria may continue for several years Until recently it was thought that when these had subsided the disease was no longer active But recent evidence suggests that some patients may develop chronic glomerular nephritis having been through a period without proteinuria There is no evidence that the severity of the acute renal failure the persistence of the disease after the acute phase or its recurrence many years later can be influenced by any therapeutic maneuver

It is customary to keep the patient in bed while he is unwell and to allow him to get up when he feels better It is an unnecessary interference with his liberty to do more Persistent microscopic

ematuria becomes more pronounced on standing nd on mobilization but unless there are other ndications of a relapse such as a rise in blood ressure a gain in weight or a deterioration of renal function this should be ignored

Finally the urine of a high proportion of patients with acute glomerular nephritis is infected usually with E coli If renal function is not too severely impaired the large amounts of penicillin which are administered to treat the streptococcal infection should be sufficient to sterilize the urine But it is well to make sure

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Clinical pharmacology of the new beta-adrenergic blocking drugs Part 6 A comparison of pindolol and propranolol in treatment of patients with angina pectoris The role of intrinsic sympathomimetic activity

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The sympathetic nervous system through its beta adrenergic actions markedly influences myocardial oxygen requirements by accelerating the heart rate and enhancing myocardial contractility A major advance in the symptomatic treatment of angina pectoris occurred with the clinical introduction of beta adrenergic blocking agents which block these sympathetically medicated effects

Four main factors--heart rate ventricular systolic pressure rate of rise of left ventricular pressure (speed of left ventricular contraction) and the size of the left ventricle--influence oxygen demand by the left ventricle Heart rate and systolic pressure seem the most important since it has been shown that their product in any individual patient with angina pectoris ne ded to be the same whether angina occurred spontaneously or was precipitated by exercise[3] As β blocking drugs reduce the increment in heart rate with exercise and allow a longer time for diastolic filling β blockade also reduces the rise of blood pressure on exercise, the velocity of cardiac contraction and the oxygen consumption at any given workload[4,5] When myocardial oxygen requirements are decreased, this results in increased exercise tolerance and decreased frequency of angina attacks β blocking drugs also have other actions (on platelets and metabolism) which may play a part in their antianginal action[6,7]

Propranolol a β adrenoceptor blocker has been proved effective in many patients with angina pectoris The drug is a non selective beta blocker with membrane depressant effects and no intrinsic sympathomimetic activity The drug is contraindicated in patients with active asthma and congestive heart failure conditions which can be aggravated by propranolol[8-11]

Pindolol (LB 46) is a new beta adrenoceptor blocking drug with the most pronounced intrinsic sympathomimetic activity (partial agonist property) of β blocking agents currently available

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As a β blocker it is four to five times more potent (milligram for milligram) than propranolol,[9] and has been shown to be an effective anti arrhythmic,[12] antihypertensive,[1] and anti anginal agent.[1] It is still debated however whether the presence of intrinsic sympathomimetic activity constitutes an advantage or disadvantage in cardiac therapy. It has been claimed by some investigators that intrinsic sympathomimetic activity protects against cardiac failure,[1] severe bradycardia,[1] and bronchial asthma.[1] On the other hand many investigators believe that intrinsic sympathomimetic activity may partially negate the therapeutic benefit of beta adrenergic blockade.[1]

The purpose of this study was to compare the clinical effectiveness of two beta blocking agents (pindolol, a drug with intrinsic sympathomimetic activity, and propranolol, a drug lacking this property) in patients with angina pectoris. The effects of the two drugs on the following parameters were compared: (1) angina attack frequency, (2) exercise tolerance measured by treadmill testing, (3) left ventricular function measured by echocardiography. Also studied were the comparative effects of gradual drug withdrawal in patients after chronic therapy.

Methods

Patients. Forty-one patients with angina pectoris due to ischemic coronary artery disease were entered in the study. There were 35 male and 6 female patients; the average age was 55 years (range 38 to 78 years). The diagnosis of coronary disease was established by coronary angiography in 33 patients (a stenosis compromising the lumen of at least one major coronary artery by more than 75%) or by a previously documented myocardial infarction (appearance of new pathological ECG Q waves, compatible clinical history, and elevation of SGOT and CPK to at least twice the normal values). In addition, every patient had a positive treadmill exercise test showing at least a 1 mm. ECG ST segment depression of the ischemic type in association with typical angina pectoris pain.

Additional criteria for inclusion were (1) at least five attacks of angina pectoris/2 weeks for three months with no evidence for an accelerated course and (2) absence of co-existent valvular heart disease, congestive heart failure, hypertension, bronchial asthma requiring continued treatment with bronchodilators, severe bradycardia (resting heart rate <50 beats/minute), intermittent claudication, and either myocardial infarction or a coronary artery bypass within 3 months.

None of the patients received beta blockers other than the study medication, long acting nitrates, tranquilizers, or sedatives. Informed consent was given in all instances.

Experimental design. The study was divided into three periods.

1. A four week run in period during which all patients took propranolol, 10 mg. orally four times a day in single-blind fashion.

2. Randomization in double-blind fashion was then carried out with patients divided into two treatment groups (8 weeks). The first group received pindolol (n = 23) in increasing oral doses 2.5 mg. four times a day for 2 weeks, 5 mg. four times a day for 2 weeks, and then 10 mg. four times a day for 4 weeks. The second treatment group received oral propranolol (n = 18), 10 mg. four times a day for 2 weeks, 20 mg. four times a day for 2 weeks, and 40 mg. four times a day for 4 weeks.

3. At the end of the last four week treatment interval, the medications were gradually tapered (double-blind) to 0 over a period of 2 weeks using the following regimen:

Days 1-4: pindolol 5.0 mg q 6.h., propranolol 20 mg q 6.h.

Days 5-8: pindolol 2.5 mg q 6.h., propranolol 10 mg q 6.h.

Days 9-12: pindolol 2.5 b.i.d., propranolol 10 mg b.i.d.

Days 13-14: pindolol 2.5 mg once daily, propranolol 10 mg once daily.

Methods of observation. All patients kept a detailed daily record of the angina attacks they experienced, the number of nitroglycerin tablets taken, and an estimation of the physical activity for that day. Every two weeks the patient were evaluated with a detailed history and physical examination and two treadmill exercise tests were performed 15 minutes apart. The second exercise test was used for analysis. Sixteen patients underwent serial resting echocardiographic studies at two week intervals. Complete blood counts, urinalyses, chest roentgenograms, resting electrocardiograms, de ... of serum antinuclear antibody ... blood screens (total protein, al

phosphate cholesterol uric acid blood urea nitrogen glucose sodium potassium total bilirubin alkaline phosphatase SGOT SGPT CPK LDH CO_2, chloride) were performed at entry at the end of the run in period and at the end of the treatment interval

Exercise tests Multistage exercise testing was performed with the use of a treadmill Patients were studied biweekly with duplicate studies in the post absorptive period according to the following protocol

At 1 mile per hour at 0 degrees elevation for three minutes

At 1 mile per hour at 10% grade for three minutes

At 1.5 miles per hour at 10% grade for three minutes

At 2 miles per hour at 12% grade for three minutes

At 3 0 miles per hour at 15% grade for three minutes (9 mets)

At 3 0 miles per hour at 17% grade for three minutes

At 3 4 miles per hour at 20% grade for three minutes (13 mets)

At 4 miles per hour at 22% grade for three minutes

At 4.5 miles per hour at 24% grade for three minutes and

At 5 miles per hour at 26% grade for three minutes

The blood pressure was measured every 3 minutes by the auscultatory method and the ECG was monitored on the oscilloscope The end point of exercise was angina pectoris defined by the patient's typical and characteristic chest pain discomfort Several patients receiving beta blockers did not develop angina and were forced to stop because of excessive fatigue An abnormal electrocardiographic response was defined as a flat or downsloping ST segment depression of 1 mm of 0 08 sec duration after the terminus of the QRS complex with the P Ta segment as the baseline of reference

Work performance was expressed in mets correlating with the level of exercise achieved on the treadmill. The product of heart rate and systolic blood pressure an indirect index of myocardial oxygen consumption was calculated from measurements obtained at the exact end point of exercise

Echocardiograms Serial echocardiographic studies were obtained in 16 patients [illegible] exercise testing These were obtained [illegible] patients in the supine position using a Hoffrel [illegible] C echocardiograph with a 2.25 mHz trans[illegible] focused at 7.5 cm

Minor axis end-diastolic dimension was measured at the point where posterior wall endocardium and septum were maximally separated [illegible] end-systolic dimension was measured at the point where they approached each other [illegible] The left ventricular dimensions measured by ultrasound have been found to approxim[illegible] closely the left ventricular minor axis in [illegible] anteroposterior projection both at end-dias[illegible] and end systole For calculation of left ventricular volume the heart was assumed to be a sphe[illegible] End-diastolic and end-systolic volumes were calculated as the cube function of the minor axis end-diastolic and end systolic diameters, respectively Ejection fraction was obtained by subtracting end systolic from end-diastolic volume and dividing this value by the end-dias[illegible] volume In all instances several cardiac cycles were analyzed and mean values were calculated This method is limited by the inability of the ultrasonic beam to scan the entire ventricle [illegible] that only a limited portion of this chamber [illegible] examined Consequently the performance [illegible] nonvisualized areas is unknown and [illegible] to inaccuracies of the technique in patients [illegible] left ventricular asynergy However in sele[illegible] patients determinations of volume and ejection fraction have proved valuable particularly [illegible] serial measurements are made in the same patient [illegible]

Statistical analysis Group means are presented with the standard error of the mean as [illegible] index of dispersion. Results were entered [illegible] IBM 370/168 computer and were analyzed [illegible] the SPSS statistical package Differences were calculated by two-way analysis of variance.

Results (Table I)

Effects of angina attack frequency (Fig 1) [illegible] the peak pindolol dose (10 mg every six hours) the mean number of angina pectoris attacks per [illegible] the mean number of angina pectoris attacks [illegible] weeks decreased from 18 4 ± 2.8 during the [illegible] period to 10 7 ± 2.2 ($p < 0 01$) At the peak propranolol dose (40 mg every six hours) the biweekly attack frequency decreased from 28.5 ± 5 1 to 15 1 ± 3 6 ($p < 0 02$) A differ[illegible] effect of propranolol and pindolol on the [illegible]

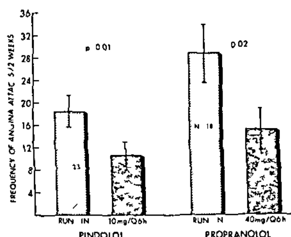


Fig 1 A significant decrease in the frequency of anginal attacks at 2 weeks is seen with both pindolol 40 mg /day and propranolol 160 mg /day compared to the run in period There was no significant difference in the effectiveness of the two drugs in reducing the frequency of anginal attacks

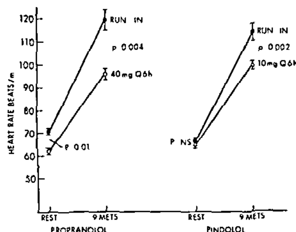


Fig 2 Effects of pindolol and propranolol on the heart rate at rest and during exercise *(9 mets)* A significant decrease in the resting heart rate and the heart rate increment with exercise is seen with propranolol (160 mg /day) compared to the run in period There is no change in the resting heart rate in patients treated with pindolol (40 mg /day) however the heart rate increment with exercise is significantly blunted

Table I The effects of pindolol and propranolol on hemodynamic functions and exercise tolerance

	Pindolol	*Propranolol*
Resting heart rate	↔	↓
Resting blood pressure	↓ ↔	↓ ↔
Resting double product	↓	↓ ↓
Rate of heart rate increase with exercise	↓	↓
Rate of systolic blood pressure increase with exercise	↓	↓
Rate of HR × BP increase with exercise	↓	↓
Resting ejection fraction (Echo)	↔	↓
Resting end-diastolic volume (Echo)	↑ ↔	↑
Exercise tolerance	↑	↑

tion in frequency of anginal attacks per 2 weeks was not observed when the data were analyzed by analysis of variance Thus pindolol and propranolol (in the doses used) are equally effective in the symptomatic relief of patients with angina pectoris

During the active treatment phase of the study no patient had an exacerbation of his/her angina attack frequency

Effects of pindolol and propranolol on resting heart rate blood pressure and double product (HR × BP) (Figs 2 to 4 Table I) At peak dose propranolol decreased the resting heart rate from 70 5 ± 2 2 to 62.2 ± 2 4 beats/minute ($p < 0\ 01$) The systolic blood pressure decreased from 123 5 ± 3 7 to 116 8 ± 3 5 mm Hg Similarly the HR × BP decreased from 8 677 ± 423 to 7 338 ± 455 beats mm Hg min ' ($p < 0\ 005$) In contrast pindolol at peak dose did not appreciably decrease the resting heart rate 66 8 ± 1 9 to 64 6 ± 1 2 beats/minute P = NS The systolic blood pressure decreased slightly from 122 0 ± 3 3 to 118 ± 19 mm Hg A small and insignificant decrease in the HR × BP was seen with pindolol 8 254 ± 418 to 7 651 ± 210 beats mm Hg min ¹

Thus pindolol did not appreciably change the resting heart rate systolic blood pressure or HR × BP while a significant decrease in both resting heart rate and HR × BP was seen in patients treated with propranolol (Figs 2 to 4 Table I) By analysis of variance a more pronounced depression of resting heart rate was induced by propranolol than by pindolol

Effects of pindolol and propranolol on exercise tolerance and HR × BP Exercise performance on the treadmill improved in both the propranolol and pindolol groups (Fig 5) In the 23 patients receiving pindolol 10 mg every 6 hours the exercise capacity of patients improved from 8 0 ± 0 4 to 9 7 ± 0 3 mets ($p < 0\ 01$) while the exercise capacity of the 18 patients on propranolol 40 mg every 6 hours improved from 8 1 ± 0 4 to 9 6 ± 0 3 mets ($p < 0\ 05$) Similarly the

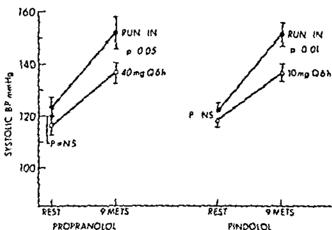


Fig 3 Effects of pindolol and propranolol on the systolic blood pressure at rest and during exercise (9 mets) There is a slight but insignificant drop in systolic blood pressure seen with both pindolol and propranolol compared to the run in period The systolic blood pressure increment with exercise is similarly blunted in both pindolol and propranolol treated patients compared to the run in period

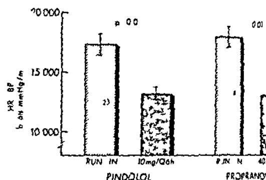


Fig 4 Effects of pindolol and propranolol on the HR at rest and during exercise (9 mets) A significant dec resting HR × BP is seen with propranolol (160 m compared to the run in period The rate of incr HR × BP during exercise was blunted with proprano mg /day) compared to the run in period A slight but i icant decrease in resting HR × BP is seen with pindo mg /day) compared to the run in period. The rate of i in HR × BP during exercise is blunted with pindo mg /day) compared to the run in period

HR × BP at the end point of the exercise decreased from 17,540 ± 827 to 15 276 ± 736 beats mm Hg min ¹ with pindolol ($p < 0.01$) 17 182 ± 1064 to 14 561 ± 963 beats mm Hg min ¹ with propranolol ($p < 0.001$) Although all patients had developed angina at the end point of exercise during the run in phase at peak dose none of 23 patients on pindolol and 10 of 18 patients on propranolol were forced to stop exercising because of fatigue and dyspnea rather than by angina

Using analysis of variance there were no differences seen between propranolol and pindolol regarding β blocker induced changes in exercise tolerance and decrements in HR × BP at exercise end point

Effects of pindolol and *propranolol* on patients exercising at a given exercise level (9 mets) When patients were exercising at the same level (9 mets) the magnitude of the exercise induced ECG ST segment depression decreased from 1 3 ± 0 3 mm during the run in period to 0 4 ± 0 15 mm in patients receiving pindolol ($p < 0.05$) and from 1 3 ± 0 3 to 0 8 ± 0 2 mm ($p < 0.05$) in patients receiving propranolol (Fig 6) Using analysis of variance there was no difference between pindolol and propranolol in their effects on the exercise induced ECG ST segment depression

At 9 mets the heart rate of patients receiving pindolol decreased from 114 2 ± 4 1 (run in) to 99 5 ± 2 9 beats/minute (pindolol 10 mg e hours) $p < 0.002$ The heart rate of pa receiving propranolol decreased from 119 6 (run in) to 95 7 ± 2 3 beats/minute (propr 40 mg every 6 hours) $p < 0.004$ At 9 me systolic blood pressure decreased from 151 8 (run in) to 132 7 ± 2.3 mm Hg (pindolol 1 every 6 hours) $p < 0.01$ and from 152.7 (run in) to 137.8 ± 3 3 mm Hg in patients r ing propranolol (40 mg every 6 hours) p < (Figs 2 and 3)

At the 9 met exercise level the HR decreased from 17 420 ± 850 (run in) 13 205 ± 510 beats mm Hg min ¹ in pa receiving pindolol 10 mg every 6 ($p < 0.002$) Similarly the HR × BP decr from 18,106 ± 840 (run in) to 13 255 ± 480 mm Hg min ¹ ($p < 0.01$) in patients rec propranolol 40 mg every 6 hours (Fig 4) was no significant difference by analysis of ance between propranolol and pindolol on effect on heart rate blood pressure, HR × BP at the 9 met exercise level

Withdrawal of pindolol and propranolol increase in the frequency of angina at occurred in both treatment groups during the week withdrawal period However we did observe death myocardial infarction or unst angina requiring hospitalization in any patie

Echocardiographic measurements (Tabl The echocardiographically measured end-

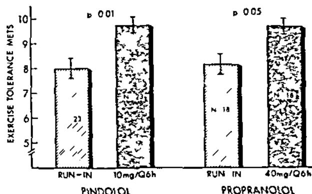


Fig 5 Effects of pindolol and propranolol on exercise tolerance in patients with angina pectoris. A significant improvement in mean total work performance occurs with both pindolol and propranolol compared to the run in period.

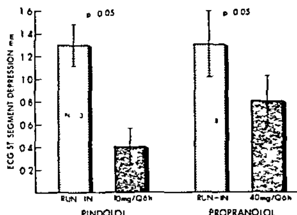


Fig 6 Effects of pindolol and propranolol on the ECG ST segment at the 9 met exercise level. There is a significant reduction in the degree of ST segment depression in pindolol and propranolol treated patients compared to the run in period

tolic volume measured at rest showed an increase after pindolol (10 mg/every 6 hours) from 70.8 ± 1.8 (run in) to 80.2 ± 2.8 ml/M², $p < 0.02$ A more pronounced increase in end diastolic volume was seen in patients receiving propranolol (40 mg/every 6 hours) from 71.8 ± 3.2 (run in) to 92.2 ± 1.9 ml/M $p < 0.003$ (Fig 7)

The echocardiographically estimated ejection fraction increased slightly in patients receiving pindolol (10 mg every 6 hours) compared to the run in period 0.59 ± 0.02 to 0.62 ± 0.02 $p < 0.02$ In contrast propranolol (40 mg every 6 hours) decreased the ejection fraction from 0.57 ± 0.02 (run in) to 0.51 ± 0.01 $p < 0.04$ (Fig 8)

Using analysis of variance the more pronounced increase in end diastolic volume induced by propranolol as compared to pindolol was significant ($p < 0.03$) The differential effect of pindolol and propranolol on the resting ejection fraction was also significant ($p < 0.002$)

Side effects The frequency and types of side effects seen with pindolol and propranolol treatment are listed in Table II Fatigue was a significant side effect seen in eight of 18 patients treated with propranolol This adverse reaction was not seen in patients treated with pindolol

Discussion

Beta adrenoceptor blocking drugs have been the greatest advance in the pharmacologic treatment of angina pectoris since nitrates were introduced 100 years ago These agents work by reducing the heart rate thus decreasing myocardial oxygen demands and allowing more time for diastolic coronary artery perfusion [5] β blockade also reduce the sympathetically mediated rise in blood pressure with exercise and the velocity of cardiac contraction Patients treated with these agents can do more exercise at a lower heart rate-blood pressure product (an indirect measure of myocardial oxygen consumption) [6]

Propranolol has proved effective in most patients with angina pectoris The drug is a non cardioselective (affecting both β_1 and β receptors) beta blocker with membrane depressant effects and lacks intrinsic sympathomimetic activity Propranolol is contraindicated in patients with active asthma and congestive heart failure since these conditions may be aggravated

Pindolol (LB 46) is a new beta adrenoceptor blocking drugs with the most pronounced intrinsic sympathomimetic activity (partial agonist activity) of agents currently available [1] Studies in reserpinized and adrenalectomized animals have shown that pindolol possesses this partial agonist effect unrelated to its β blocking properties [2] Pindolol is non-cardioselective and has weaker membrane depressant activity than propranolol [8, 3] Unlike propranolol, it lacks first pass metabolism

The drug has been shown in multiple clinical trials to be an effective anti arrhythmic [1-3] anti hypertensive [1, 31] and anti anginal agent [1, 32] Despite pindolol s proven clinical effectiveness, it has still not been determined whether intrinsic

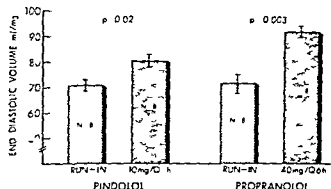


Fig 7 Effects of pindolol and propranolol on the left ventricular end-diastolic volume fraction determined from the echocardiogram Compared with the run in period there is a significant increase in end-diastolic volume with pindolol (40 mg./day) and propranolol (160 mg./day) The increase in end-diastolic volume with propranolol is significantly greater than that seen with pindolol.

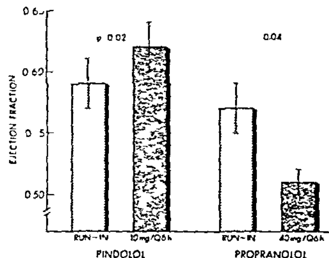


Fig 8 Effects of pindolol and propranolol in the left ventricular ejection fraction determined from the echocardiogram Compared with the run in period, there is a slight but significant increase in the ejection fraction with pindolol (40 mg day) and a decrease in this parameter with propranolol (160 mg. day) The effects of pindolol and propranolol on the ejection fraction are significantly different

sympathomimetic activity is advantageous or disadvantageous in cardiac therapy This partial agonist property has been claimed by some investigators to protect against myocardial failure however comparative studies using compounds with (alprenolol) and without this property have revealed conflicting results It is known that compounds with intrinsic sympathomimetic activity produce less depression of atrioventricular conduction [35] and smaller elevations of peripheral vascular resistance for a given degree of be. receptor blockade [34] Similarly agents which a devoid of intrinsic sympathomimetic activ depress the resting heart rate more readily th do those agents with this property

Some clinical investigators have postul.. that intrinsic sympathomimetic activity wo detract from beta blockade and therefore ne any therapeutic effectiveness in patients. results show that pindolol and propranolol a equally effective in patients with angina pecto when equipotent doses are used (pindolol 10 m orally four times daily propranolol 40 mg oral four times daily) Both drugs reduce the freque cy of angina pectoris attacks and improve exerc tolerance At a comparable exercise level (9 met there were similar effects of both drugs on th ECG ST segment systolic blood pressure he rate and heart rate-blood pressure product, wh compared to the run in period Thus both pind lol and propranolol are equally efficacious improving exercise tolerance in patients, while the same time reducing their myocardial oxyge demands

At rest pindolol and propranolol had simil effects on the systolic blood pressure howeve pindolol had no appreciable effect on rest heart rate in contrast to propranolol where marked reduction in this parameter was note The rate-pressure product though not signi cantly different with the two drugs tended to b lower with propranolol (related to its gre rate-lowering effects)

An explanation for the similar effects of th drugs seen at exercise and the differences at re probably relates to the intrinsic sympathomime ic activity of pindolol Intrinsic sympathomime activity should be more pronounced at rest (in state of decreased sympathetic tone) and a increase in heart rate secondary to this propert would counterbalance a decrease in rate cause by beta blockade Thus the resting heart rat would not change with pindolol (as shown in th study) whereas propranolol (lacking a ... activity) would decrease the resting heart rate However during exercise where there is marke sympathetic stimulation the beta blocking ef fects of pindolol would be more pronounced a would markedly outweigh the direct stimulato effects of intrinsic sympathomimetic activ which is a factor dependent on dose and not on underlying sympathetic tone Thus, in states of

high adrenergic activity all β adrenoceptor blocking drugs should be equally efficacious (whether or not they have intrinsic sympathomimetic activity) a fact that has been borne out by clinical trials demonstrating the clinical effectiveness of all β blocking agents in exercise-induced angina pectoris [10]

Pindolol was also shown from echocardiographic studies done at rest to be less of a myocardial depressant than propranolol Pindolol was shown to cause a slight increase in the echocardiographically determined ejection fraction and end diastolic volume Propranolol caused a decrease in ejection fraction and a greater increment in end diastolic volume

The greater resting end diastolic volume increment with propranolol may have been related to its rate lowering effects and a greater time for diastolic filling The maintenance of the resting ejection fraction with pindolol probably results from its stimulating intrinsic sympathomimetic activity counteracting the negative inotropic effects of beta adrenoceptor blockade in a low adrenergic state In contrast propranolol lacking partial angonist activity slightly depressed the ejection fraction at rest Whether or not the effects on the ejection fraction would differ between propranolol and pindolol in the hyperadrenergic state seen with exercise has yet to be determined One could speculate that the drugs in the setting of intense exercise and increased sympathetic tone would behave in a similar fashion (intrinsic sympathetic activity should no longer be important)

Recently great attention has been directed towards the dangers of abrupt beta blocker withdrawal in patients with angina pectoris [3, 7] In this study both pindolol and propranolol were safely withdrawn using the gradual withdrawal regimen described in the methods section However all the patients in the pindolol and propranolol treatment groups had a recrudescence of their angina pectoris symptomology when the drug was gradually withdrawn However no patient developed unstable or crescendo angina requiring hospitalization an acute myocardial infarction or sudden death Thus beta adrenoceptor blocking drugs can be safely withdrawn after chronic therapy if this is done in a gradual fashion

Regarding adverse reactions pindolol is a relatively safe drug that differs from propranolol by causing less fatigue in patients Whether this

Table II Adverse reactions seen in patients treated with pindolol (N = 23) and propranolol (N = 18)

Pindolol		*Propranolol*	
Nature of reaction	*Number of patients*	*Nature of reaction*	*Number of patients*
Nasal stuffiness	1	Rash	1
Nocturia	1	Blurred vision	2
Impotence	1	Fatigue	8
Palpitations	1	Dyspnea on exertion	1
Total with adverse reactions	4	Mild hypotension	5
		Total with adverse reactions	17

observation is related to the presence of intrinsic sympathomimetic activity is still only speculative

Pindolol with its intrinsic sympathomimetic activity is an effective alternative to propranolol in patients with exercise induced angina pectoris Pindolol would appear to be more advantageous than propranolol in patients with resting sinus bradycardia where the latter drug might be contraindicated Pindolol might also be a safer beta adrenoceptor blocking agent in patients with angina pectoris and mild to-moderate congestive heart failure Pindolol can also be substituted for propranolol where fatigue is a problem with the latter drug From studies done in patients with supraventricular arrhythmias and bronchospasm it might also appear to be a better agent in patients with both angina pectoris and bronchial asthma [illegible] On the other hand pindolol does not lower the resting heart rate of patients Therefore in patients who have angina pectoris at rest or at low exercise levels propranolol would probably be more effective

In conclusion intrinsic sympathomimetic activity does not interfere with the therapeutic effectiveness of pindolol in exercising patients with angina pectoris This property might also provide a protective effect in patients with unacceptable bradycardia or with congestive heart failure at rest

Thus there are real differences between pindolol and propranolol which might be clinically useful reinforcing the need to have multiple

beta adrenoceptor blockers available to the practicing physician

Summary

Pindolol a new beta adrenergic blocking drug with intrinsic sympathomimetic activity, and propranolol were given in increasing equipotent doses (pindolol 2 5 to 10 mg every 6 hours propranolol 10 to 40 mg every 6 hours) over 12 weeks in a double blind randomized trial to 41 patients with angina pectoris The drugs were then gradually withdrawn over a two week period With maximum doses both pindolol and propranolol increased exercise capacity, compared to control on multistage treadmill testing (pindolol $8 0 \pm 0 4$ to $9 7 \pm 0 3$ mets $p < 0 01$ propranolol $8 1 \pm 0 4$ to $9 6 \pm 0 3$ mets $p < 0 05$) At each exercise level both pindolol and propranolol decreased the heart rate systolic blood pressure and rate-pressure product (HR × BP) At the 9 met exercise level the HR × BP decreased from $17 420 \pm 850$ to $13 205 \pm 510$ mm Hg min^{-1} with pindolol ($p < 0 002$) with propranolol $18,106 \pm 440$ to $13 225 \pm 480$ mm Hg min^{-1} ($p < 0 01$) At the same level the magnitude of exercise induced ECG ST depression decreased from $1 3 \pm 0 3$ to $0 4 \pm 0 15$ mm with pindolol ($p < 0 05$) and from $1 3 \pm 0 3$ to $0 8 \pm 0 2$ mm with propranolol ($p < 0 05$) Both drugs reduced the number of spontaneous attacks of angina pectoris per week Pindolol did not appreciably decrease the resting heart rate ($66 8 \pm 1 9$ vs $64 6 \pm 1 2$) or HR × BP ($8 254 \pm 418$ vs $7 651 \pm 210$ mm Hg min^{-1}) in contrast to propranolol which reduced both (heart rate $70 5 \pm 2 2$ to $62 2 \pm 2 4$ $p < 0 01$ HR × BP $8 677 \pm 423$ to $7 338 \pm 455$ mm Hg min^{-1} $p < 0 005$) In addition pindolol slightly increased the echocardiographically estimated ejection fraction at rest ($0 59 \pm 0 02$ to $0 62 \pm 0 02$ $p < 0 02$) while propranolol depressed it ($0 57 \pm 0 02$ to $0 51 \pm 0 01$ $p < 0 04$) Both pindolol and propranolol could be safely withdrawn over a gradual two week withdrawal interval

Conclusions (1) Both pindolol and propranolol are effective in the symptomatic relief of angina pectoris (2) Pindolol is preferable in patients with resting bradycardia or congestive heart failure while propranolol may be more effective in patients with angina at rest or at very low exercise levels (3) The two drugs can be safely withdrawn (if this is done in a gradual fashion. (4) Intrinsic sympathomimetic activity does not interfere with the therapeutic benefit of beta blockade in angina pectoris

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beta adrenoceptor blockers available to the practicing physician

Summary

Pindolol a new beta adrenergic blocking drug with intrinsic sympathomimetic activity and propranolol were given in increasing equipotent doses (pindolol 2 5 to 10 mg every 6 hours propranolol 10 to 40 mg every 6 hours) over 12 weeks in a double blind randomized trial to 41 patients with angina pectoris The drugs were then gradually withdrawn over a two week period With maximum doses both pindolol and propranolol increased exercise capacity compared to control on multistage treadmill testing (pindolol 8 0 ± 0 4 to 9 7 ± 0 3 mets $p < 0 01$ propranolol 8 1 ± 0 4 to 9 6 ± 0 3 mets $p < 0 05$) At each exercise level both pindolol and propranolol decreased the heart rate systolic blood pressure and rate-pressure product (HR × BP) At the 9 met exercise level the HR × BP decreased from 17 420 ± 850 to 13 205 ± 510 mm Hg min^{-1} with pindolol ($p < 0 002$) with propranolol 18 106 ± 440 to 13 225 ± 480 mm Hg min ($p < 0 01$) At the same level the magnitude of exercise induced ECG ST depression decreased from 1 3 ± 0 3 to 0 4 ± 0 15 mm with pindolol ($p < 0 05$) and from 1 3 ± 0 3 to 0 8 ± 0 2 mm with propranolol ($p < 0 05$) Both drugs reduced the number of spontaneous attacks of angina pectoris per week Pindolol did not appreciably decrease the resting heart rate (66 8 ± 1 9 vs 64 6 ± 1 2) or HR × BP (8 254 ± 418 vs 7 651 ± 210 mm Hg min) in contrast to propranolol which reduced both (heart rate 70 5 ± 2 2 to 62 2 ± 2 4 $p < 0 01$ HR × BP 8 677 ± 423 to 7 338 ± 455 mm Hg min^{-1} $p < 0 005$) In addition pindolol slightly increased the echocardiographically estimated ejection fraction at rest (0 59 ± 0 02 to 0 62 ± 0 02 $p < 0 02$) while propranolol depressed it (0 57 ± 0 02 to 0 51 ± 0 01 $p < 0 04$) Both pindolol and propranolol could be safely withdrawn over a gradual two week withdrawal interval

Conclusions (1) Both pindolol and propranolol are effective in the symptomatic relief of angina pectoris (2) Pindolol is preferable in patients with resting bradycardia or congestive heart failure while propranolol may be more effective in patients with angina at rest or at very low exercise levels (3) The two drugs can be safely withdrawn (if this is done in a gradual fashion (4) Intrinsic sympathomimetic activity does not interfere with the therapeutic benefit of beta blockade in angina pectoris

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treated routinely with the procedure Transiently severe bradycardia mi ht present a potential hazard in patients receiving propranolol as well although to date we have encountered no problem in several such individuals Finally patients with the permanent or chronic form of reciprocating AV junctional tachycardia whose PSVT responds poorly to vagal stimulation are not good candidates for the diving reflex, of course For most acute episodes of vagoresponsive PSVT however the diving reflex offers a safe simple and useful mode of treatment that deserves a place in the standard therapeutic approach to the syndrome

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Sulfinpyrazone after myocardial infarction

The recent report of a reduction in sudden deaths after myocardial infarction in patients treated with sulfinpyrazone is at first sight rather surprising Indeed the title of the study the Anturane Reinfarction Trial suggests that the investiga tors were expecting the antithrombotic effects of sulfinpyra zone to protect their patients from further myocardial infarc tion but this has not yet been demonstrated However myocardial infarction is not always attributable to occlusive thrombosis within the coronary arteries and it is worth considering other possible explanations for the reduction in sudden deaths It has been suggested that the drug reduced the rate of platelet/fibrin emboli within the coronary vascula ture and in so doing prevented the development of fatal cardiac arrhythmias This seems to be a tenable hypothesis since as we shall see sulfinpyrazone has been shown to affect both platelets and also fibrin which are the main components of so called white thrombus White thrombus forms in areas of high blood flow rate and shear stress and may occur within the arterial circulation and also on the surfaces of foreign materials such as artificial heart valves and dialyser membranes Its depo ition seems to be affected little by anticoagulants such as heparin or warfarin a fact which may explain the ineffectiveness of these agents after myocardial infarction Sulfinpyrazone is a uricosuric agent and it was noted that it restored after several weeks administration shortened platelet survival to normal in gouty subjects with thromboembolic disorders It also prolongs platelet survival in rabbits a species with very low serum uric acid levels which led Mustard and associates to suppose that its antiplatelet action was independent of its uricosuric effects Although the drug inhibits platelet aggregation in the test tube the concen trations required seem to be higher than those likely to be attained with in vivo use However inhibition of collagen induced aggregation has been shown in vivo and the small but statistically significant prolongation of bleeding time demonstrable with careful study after only two days admin istration to healthy volunteers suggests that in therapeutic dosage it does indeed have some inhibitory effect on the interaction between platelets and vascular endothelium Although the Anturane Reinfarction Trial Research Group

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reported no prolongation of bleeding time in patients receiving sulfinpyrazone it is unlikely that the observations of this in vivo test of platelet function were made by the same observer in any one patient a condition which we found to be necessary to demonstrate an effect

It is not clear whether the reduction of fibrin on dialysers that we have demonstrated recently is mediated by sulfinpyrazone s action on platelets or by other mechanisms Since the patients in these studies were to all intents and purposes anephric the uricosuric action of the drug seems to be unimportant and any effect it may have on the endothelium irrelevant Perhaps the fibrin in white thrombi is derived from the platelets themselves or its deposition may be mediated by platelet factors the release of which sulfinpyrazone inhibits but which heparin and warfarin fail to influence In another study of the effects of sulfinpyrazone during use of charcoal hemoperfusion we concluded that sulfinpyrazone reduced the stability of platelet aggregates and it is interesting now to note Relman invoking a similar mechanism to explain the reduction of sudden deaths with use of sulfinpyrazone after myocardial infarction

Ali and McDonald have proposed inhibition of platelet prostaglandin synthesis as the mechanism by which sulfinpyrazone acts This observation invites an inevitable but interesting comparison with aspirin which inhibits platelet thromboxane synthesis and also vessel wall synthesis of the potent anti aggregant prostacyclin A single 300 mg dose of aspirin inhibits platelet function for up to 10 days but many trials of aspirin s antithrombotic potential have been carried out at much higher dosages which may have masked any benefit by blocking vessel wall prostacyclin synthesis Is the same true of sulfinpyrazone? And if so is the 800 mg /day dose correct? Unlike aspirin sulfinpyrazone doe not increase occult gastrointestinal blood loss in healthy volunteers an effect which aspirin may mediate by inhibition of gastric prostaglandin synthesis and we await reports of sulfinpyrazone s effects on vessel wall prostaglandin synthesis with interest One wonders whether the organizers of large clinical trials of antithrombotic agents would repeat their investigations in the light of more optimum dosage schedules suggested by their pharmacological colleagues as for example with aspirin and dipyridamole? Should other drugs that have been shown to have an inhibiting effect on platelets be subjected to clinical trials? The choice of appropriate drug and dosage schedule have no doubt deterred many trial organizers but the Anturane Reinfarction Trial Research Group deserve congratulations both for their endeavours and al o for their prompt and honest reporting of what may have been a surprise finding One hopes that the trial will proceed to its conclusion and no doubt it will serve as a model for many trials of antithrombotic agents to come

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Of bends cardiomyopathy

People who work under pressures above atmo pheric pressure such as divers must return to atmospheric pressure slowly and properly In those who are careless and who attempt to be decompressed rapidly because of impatience poor management or equipment failure bubbles of air are released throughout the body including the myocardium The earliest

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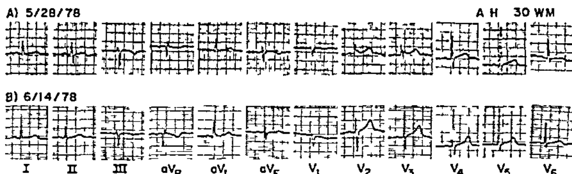


Fig 1 Serial electrocardiograms of a 30-year old man who developed "bends" cardiomyopathy The tracing in *A* was recorded during the bends, whereas the tracing in *B* was recorded after full recovery Note the changes in the QRS complex ST segment and T waves, particularly in Leads aVF and V V

and most subtle changes that reflect myocardial injury occur in the configuration of the time course of the ST segment and T wave of the electrocardiogram (Fig 1) These mild changes rapidly reverse to normal if the damage is detected early and is not too extensive and if the subjects are rapidly recompressed Extensive damage can occur with extremely rapid decompression or with repeated attacks of bends Cardiac discomfort similar to angina pectoris could possibly occur but most of the discomfort is in the skeletal muscles and joints and headaches.

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Pathology of coronary artery bypass graft surgery*

Coronary artery bypass surgery is creating a new form of heart disease with considerably altered coronary anatomy Detailed understanding of the morphology of the heart after coronary bypass surgery is important to sorting out the success or failure of this procedure A pathologic study of coronary bypass surgery includes evaluation of the anastomosis sites changes in the implanted bypass graft per se and an assessment of the effects of this procedure on the myocardium

Most graft occlusions occur at the coronary artery graft anastomosis site and the mechanisms responsible are predominately *thrombosis* and *compression* of the lumen by the suture line Although some thrombotic deposition almost always occurs at the anastomosis site why in some patients totally occlusive thrombi develop is not clear Endarterectomy of the native coronary artery is one factor which appears to predispose to thrombosis trauma to the vein itself at the time of its preparation may be another Compression of the anastomosis site is seen usually when the native vessel is of small caliber and has insufficient wall to be taken up in a suture line without resulting in lumenal compromise This mechanism of graft failure occurs both when the native coronary artery is unduly small (< 1 mm) or when the lumen at the anastomosis site is narrowed unexpectedly by eccentric plaque Coronary arterial dissection may be a cause of anastomosis failure but it is infrequent probably because atherosclerotic changes in the coronary artery limit medial hematoma extension

Morphologic changes within the vein graft itself are of little consequence in the early course of coronary bypass surgery

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but it is likely that their fate will be one of the major determinants of the long term success or failure of this procedure All vein grafts implanted in the coronary arterial system undergo alterations which generally reflect the duration of their implantation A fine layer of platelet and fibrin thrombus deposits on the intima of the vein in response to the endothelial injury which is probably an unavoidable consequence of manipulation and preparation of the graft These laminar deposits organize and within 2 to 4 weeks virtually all grafts show intimal thickening by circumferential plaque This plaque may become infiltrated with mesenchymal cells lipid laden macrophages and may develop focal calcific deposits with all the morphologic characteristics of an atherosclerotic plaque Thus intimal hyperplasia or vein atherosclerosis especially early on is in part a normal reparative phenomenon in response to intimal injury and possibly due to continued intimal injury resulting from exposure of the vein to systemic pressures The degree to which the intimal proliferation progresses after the first several weeks is variable however and is an unsolved but exceedingly important problem to late graft patency Clinical and pathologic studies have demonstrated focal high grade occlusions virtually indistinguishable from atherosclerosis as early as one year after implantation[3] Recent clinical studies of long term follow up (> 4 years) have suggested that focal narrowings develop in the implanted grafts at a rate of .5 to 1% per year[5] Insofar as these occlusions have been shown to develop at such brief intervals this form of graft atherosclerosis appears especially accelerated and malignant Determination of risk factors important in graft atherosclerosis and interventions that might ameliorate them will be essential in determining whether this operative procedure will be curative or palliative for a given patient

A third major determinant of the success or failure of coronary bypass surgery is the effect of this procedure upon the myocardium One would expect that myocardium would be protected and infarcts prevented by a revascularization procedure but clinical angiographic studies have failed to demonstrate a consistent improvement in ventricular function after this procedure or a decreased incidence of myocardial infarction Morphologic study of 58 patients coming to autopsy with this procedure over the past 10 years suggest that one reason for this may be myocardial injury sustained in the perioperative period The myocardial necrosis which develops in this setting is of a different pathophysiologic type than that seen in the setting of a natural history myocardial infarct The latter most often occurs in the setting of an acute coronary occlusive event resulting in a coagulative infarct the former however appears to occur most frequently in the distribution of a widely patent bypassed vessel and is a hemorrhagic reperfusion type of injury The importance of this observation is that it suggests most perioperative injury occurs not as a result of graft failure or occlusion but is rather a consequence of intraoperative ischemic injury Some intra operative ischemia is an unavoidable consequence of cardio pulmonary bypass and will be most accentuated in th distribution of critically narrowed vessels which are transient ly occluded at the time of anastomosis It is hopeful that th perioperative infarct due to transient intraoperative ischem will become increasingly less frequent as methods of in n operative myocardial preservation are improved

In summary morphologic and analysis of saphenous ve bypass surgery at the present time points toward two maio problem areas One is vein graft atherosclerosis. When an why does it progress to occlusion and can it be preven ed The second is myocardial preservation in the perioperati period Will improved methods of intraoperative protectio allow greater numbers of patients to have improved le ventricular function postoperatively? These problems of gra atherosclerosis and operative myocardial injury are on whose solution will hopefully lead in time to the expected an not yet realized outcome of coronary artery bypass gra surgery prevention of myocardial infarction and prolongat of life

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Calcified mitral ring in hypertrophic cardiomyopathy

To The Editor

Drs. Krasnow and Stein in their recent report on hypertrophic cardiomyopathy in the aged show in their Fig 1 a typical echo of such a patient

In this echo what they call posterior wall" is most probably a calcified mitral ring This also may be an explanation of their comment (p 378) that they have found in eight patients a small posterior echo free space—most probably posterior to a calcified mitral ring (as in Fig 1) interpreted erroneously as a small pericardial effusion

Calcified mitral ring is a frequent finding in our population of older patients with hypertrophic cardiomyopathy It would be very interesting to know how many of Krasnow and Stein s patients demonstrated this picture

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Reply

To the Editor

In answer to the letter by Dr Glaser in reference to our article on hypertrophic cardiomyopathy in the aged we agree that our Fig 1 does show a calcified mitral ring

We have seen several such instances primarily in cases discovered after the publication of our paper The small posterior pericardial effusions we reported were however true echo free spaces posterior to the epicardium and were not confused with calcified mitral annuli

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Thallium 201—an index of peripheral arterial perfusion

To the Editor

In his very interesting and exhaustive paper (AM HEART J 97 241 1979) including both theoretical and practical considerations Dr R W Barnes has however overlooked the use of thallium 201 in peripheral vascular exploration If this radionuclide is well known mainly for the assessment of coronary artery disease and myocardial infarction some experiments have also shown that its distribution can reflect the peripheral vascularization at the level of the legs.[2] In effect under physiological conditions, its biological behavior is almost identical to that of potassium this explains why thallium 201 is rapidly cleared from the arterial blood during its first pass in muscular tissues Even if the relative myocardial uptake always remains highest the uptake of the muscular skeleton is easily detectable by a conventional scintillation gamma camera The intensity of this uptake is directly related to the blood flow so that the peripheral vascularization can be studied indirectly and qualitatively by naked eye comparison of pictures Quantitatively it can be studied by using a computer for counting activity in selected areas The main limitation of this method is that it allows only comparative studies between the two legs. But because of its innocuousness and simplicity in interpretation it can be of great utility *in any unilateral vascular disease by allowing the observation* of the evolution of the relative vascularization under medical treatment or after a surgical intervention.

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Reply

To the Editor

I appreciate Dr Maublant s pointing out the potential application of thallium 201 in providing a qualitative and potentially quantitative index of peripheral arterial perfusion in lower extremity arterial occlusive disease Although several radionuclide techniques were reviewed in my manuscript I did limit the discussion to some of the more commonly used modalities In a general review of this kind it is important to maintain a perspective about the relative cost and complexity of diagnostic methods versus the amount of information provided I believe that tests such as the thallium 201 may provide little more specific data than simpler techniques such as Doppler ultrasound and plethysmography which are much less expensive and more portable However some radionuclide techniques do provide unique information such as I 125 fibrinogen scanning for activity of venous thrombosis and xenon 133 wash-out determinations which provide quantifica

but it is likely that their fate will be one of the major determinants of the long term success or failure of this procedure All vein grafts implanted in the coronary arterial system undergo alterations which generally reflect the duration of their implantation [3] A fine layer of platelet and fibrin thrombus deposits on the intima of the vein in response to the endothelial injury which is probably an unavoidable consequence of manipulation and preparation of the graft These laminar deposits organize and within 2 to 4 weeks virtually all grafts show intimal thickening by circumferential plaque This plaque may become infiltrated with mesenchymal cells lipid laden macrophages, and may develop focal calcific deposits with all the morphologic characteristics of an atherosclerotic plaque Thus intimal hyperplasia or vein atherosclerosis especially early on is in part a normal reparative phenomenon in response to intimal injury and possibly due to continued intimal injury resulting from exposure of the vein to systemic pressures The degree to which the intimal proliferation progresses after the first several weeks is variable however and is an unsolved but exceedingly important problem to late graft patency Clinical and pathologic studies have demonstrated focal high grade occlusions virtually indistinguishable from atherosclerosis as early as one year after implantation Recent clinical studies of long term follow up (> 4 years) have suggested that focal narrowings develop in the implanted grafts at a rate of .5 to 1% per year Insofar as these occlusions have been shown to develop at such brief intervals this form of graft atherosclerosis appears especially accelerated and malignant Determination of risk factors important in graft atherosclerosis and interventions that might ameliorate them will be essential in determining whether this operative procedure will be curative or palliative for a given patient

A third major determinant of the success or failure of coronary bypass surgery is the effect of this procedure upon the myocardium. One would expect that myocardium would be protected and infarcts prevented by a revascularization procedure but clinical angiographic studies have failed to demonstrate a consistent improvement in ventricular function after this procedure or a decreased incidence of myocardial infarction Morphologic study of 58 patients coming to autopsy with this procedure over the past 10 years suggest that one reason for this may be myocardial injury sustained in the perioperative period The myocardial necrosis which develops in this setting is of a different pathophysiologic type than that seen in the setting of a natural history myocardial infarct The latter most often occurs in the setting of an acute coronary occlusive event resulting in a coagulative infarct the former however appears to occur most frequently in the distribution of a widely patent bypassed vessel and is a hemorrhagic reperfusion type of injury The importance of this observation is that it suggests most perioperative injury occurs not as a result of graft failure or occlusion but is rather a consequence of intraoperative ischemic injury Some intraoperative ischemia is an unavoidable consequence of cardiopulmonary bypass and will be most accentuated in the distribution of critically narrowed vessels which are transiently occluded at the time of anastomosis It is hopeful that the perioperative infarct due to transient intraoperative ischemia will become increasingly less frequent as methods of intraoperative myocardial preservation are improved.

In summary morphologic and analysis of saphenous vein bypass surgery at the present time points toward two major problem areas One is vein graft atherosclerosis. When and why does it progress to occlusion and can it be prevented? The second is myocardial preservation in the perioperative period Will improved methods of intraoperative protection allow greater numbers of patients to have improved left ventricular function postoperatively? These problems of graft atherosclerosis and operative myocardial injury are ones whose solution will hopefully lead in time to the expected and not yet realized outcome of coronary artery bypass graft surgery prevention of myocardial infarction and prolongation of life

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Book reviews

Cardiovascular Drugs volume one Antiarrhythmic Antihypertensive and Lipid Lowering Drugs Edited by Graeme S Avery Baltimore 1978 University Park Press 176 pages. Price $24.50

This volume on antiarrhythmic antihypertensive and lipid lowering drugs summarizes the clinical pharmacology of important cardiovascular drugs for undergraduate students and postgraduate students and for practicing physicians as well. The contributors are numerous. There is a chapter on digitalis glycosides this chapter is extremely important when it is indicated that "digitalis intoxication is one of the most common adverse drug reactions, and potentially one of the most lethal. This is a pathetic medical commentary It certainly is not the fault of digitalis glycosides but the type selected and most of all, its improper use The mortality rate is stated to be between 7 and 50% among patients intoxicated with digitalis Twenty three % of patients receiving digitalis are definitely intoxicated and 6% more are possibly intoxicated This reflects poor training in the use of digitalis Thus, does digitalis help or injure more patients? The book contains a highly selected and inadequate bibliography Nevertheless this book volume One of this series on cardiovascular drugs, is worth studying even though the clinical use of digitalis is inadequately presented This is primarily a publication on clinical pharmacology rather than on therapeutics

Cardiovascular Drugs volume two β adrenoceptor Blocking Drugs Edited by Graeme S Avery Baltimore 1978 University Park Press 176 pages Price $ 9.50

This book volume Two of the series on cardiovascular drugs, is concerned with a thorough summary of the clinical pharmacology of β adrenoceptor blocking drugs The properties of these drugs are nicely summarized in the first and second chapters The next four chapters are concerned with their use in the treatment of hypertension angina pectoris, cardiac arrhythmias and hyperthyroidism Adverse reactions, and autoimmune phenomena are discussed in the other three chapters This is a good book on an important group of drugs already proven to be valuable in therapeutics Students, house staff and practicing physicians will find this book to be worth owning for study and reference

Ischemic Heart Disease The Strategy of Postponement Edited by A. Tybjaerg Hanse M D., Peter Schnohr M.D., and Geoffrey Rose M D., Chicago 1977 An FADLs Forlag publication Distributed by Year Book Medical Publishers, Inc 272 pages. Price $14.95

This book is primarily concerned with the epidemiology and risk factors in ischemic heart disease The symposium was supported by the Danish Heart Foundation to inform the public of the risk factors in ischemic heart disease The book will interest physicians, social workers nurses, and public health workers and public health officers. The usual risk factors such as smoking blood pressure physical exercise, diet and psychological factors are discussed. The illustrations are clear and simple The ideas and illustrations should be useful for public forums, lay press, and even for medical and hospital lectures This is an interesting and useful publication It contains little new

Books received

Modern Medical Mistakes By Edward C Lambert M D Bloomington Ind 1978 Indiana University Press, 190 pages. Price $10 95

The Lung Structure Function and Disease Edited by William M Thurlbeck and Murray R Abell, Baltimore 1978 The Williams & Wilkins Company 332 pages Price $34 00

No More Butts By Richard W Olshavsky Bloomington Ind 1977 Indiana University Press 181 pages. Price $10 00

ISAM 1977 Proceedings of the Second International Symposium on Ambulatory Monitoring Edited by F D Stott E B Raftery P Sleight and L. Goulding London, New York San Francisco 1978 Academic Press, Inc., 331 pages

Establishment of the International Atherosclerosis Society (IAS)

The International Atherosclerosis Society (IAS) was orga nized to promote at the international level the advancement of science and teaching related to the field of atherosclerosis. Membership is open to all scientists who will document their studies in worthwhile research in the field Enquiries regarding application for membership should be sent to Prof Gotthard Schettler M D., President IAS Direktor der Medizinischen Universitatsklinik Bergheimer Strasse 58 D-6900 Heidelberg Germany or to Prof M Daria Haust M D Secretary Treasurer IAS Department of Pathology The University of Western Ontario London Ontario Canada

Echocardiography Courses

The Division of Diagnostic Ultrasound of Thomas Jefferson Universtiy Hospital, under the direction of Barry B Goldberg M.D is offering the following courses Basic Echocardiogra phy--November 26 30 1979 April 14 18 1980 Advanced Echocardiography--December 3 7 1979 April 21 25 1980

Invited lecturers and members of the full time staff (which includes four physicians and nine sonographers) will present an extensive lecture program The participants will also have available case review material hands on time with equip ment and an extensive videotape and reference library for after hours review The courses have Category I Credit For more information please contact Lynn Lindengrass Educa tion Secretary Division of Diagnostic Ultrasound, 1015 Walnut St Philadelphia PA 19107 Phone 215 928-8533

Symposium on Preservation of Ischemic Myocardium

On November 1 and 2 1979 the Deborah Heart and Lung Center Browns Mills N J will present a symposium en "Preservation of the Ischemic Myocardium For compl information regarding this symposium please contact Ms Ann Ramsey Symposium Coordinator 421 Horns Rd D-98 Wayne Pa 19087 Telephone (215) 688-6859

ISFC Congress and Symposium

The Scientific Councils of the International Soce y and Federation of Cardiology (ISFC) are organizing or sponsor the following meetings Fifth International Congress of Ahe osclerosis to be held in Houston Texas, on November through 9 1979 For information contact Dr A. M. Go Department of Medicine Baylor College of Medicine, The Methodist Hospital, 6516 Bertner Ave Mail Station A Houston Texas 77030 U S.A

Symposium on Cardiomyopathies to be held in Budap Hungary on November 9 and 10 1979 This symposium is also sponsored by WHO the Hungarian Society of Cardiology and the Hungarian Society of Pathology For information, contact Dr Lagos Matos, Hungarian Institute of Cardiology PO Box 9/88 Budapest Hungary

Recent Advances in Cardiopulmonary Care V

A seminar entitled Recent Advances in Cardiopulmonary Care V will be held at the Holiday Inn Lido Bea Sarasota Fla on November 2 and 3 19 9 The seminar is sponsored by Memorial Hospital Sarasota. Tuition is $60 for physicians and $40 for RNs LPNs, and respiratory therapists the fee includes two luncheons and a cocktail party Applica tion has been made to award 10 continuing education hours for physicians and nurses who attend the seminar For further information contact Deborah M Searcy RN Clinical Instructor HRD Sarasota Memorial Hospital, 1901 Arl ton St Sarasota Fla 335"9

American Heart Journal

November 1979 Volume 98 Number 5

Editorial

Home or hospital for myocardial infarction—who cares?

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J R A Mitchell M D F R C P
Nottingham England

For half a century after the recognition of the clinical syndrome of myocardial infarction physicians were concerned about the mechanical properties of the damaged heart Fears that the necrotic area would rupture or that it would impair the heart s pumping capacity led to the adoption of strict and prolonged schedules of bed rest Clinicians were advised that rest in bed for weeks or months should be prescribed in order to assure as sound a healing of the myocardial infarct as possible with very gradual and careful convalescence [1] or that Rest in bed should be continued for from six to eight weeks to ensure firm cicatrisation of the ventricular wall during the whole of this period the patient is to be guarded by day and night nursing and helped in every way to avoid voluntary movement or effort Patients have lost their lives by neglect of these precautions [2] These regimes could not of course be carried out at home so anxiety about the mechanical aspects of infarction led clinicians to believe that hospital admission was obligatory

Individual clinicians challenged this view but by the time that controlled trials had confirmed that early mobilization and discharge from hospital had no adverse effect on outcome a new justification for hospital admission was emerging—namely the electrical consequences of a heart attack It was recognized that the commonest cause of early death after myocardial infarction was ventricular fibrillation and the development of external cardiac massage and D C countershock meant that by prompt intervention an otherwise fatal arrhythmia could be corrected This led to the creation of coronary care units (CCU s) where patients liable to develop ventricular fibrillation could be observed and treated Although no adequate randomized trial of the long term value of intensive coronary care has yet been carried out and although there is evidence suggesting that patients have the same mortality rate whether they are initially admitted to a CCU or to an ordinary ward various official bodies have indicated that the provision of such units is mandatory so that all patients with suspected myocardial infarction can be admitted to them For example the Joint Working Party of the British Cardiac Society and the Royal College of Physicians[4] held the unanimous view that some form of specialised accommodation for the care of patients after cardiac infarction is essential

The community mortality rate from heart attacks has not however been reduced by the widespread development of CCU s[5] so many doctors and not a few patients have begun to ask whether the stress of transporting ill patients to hospital might not increase their risk of developing arrhythmias The work done by coronary care units could therefore merely reflect their ability to neutralize the harm done by admitting the patients to hospital in the first place

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Table 1 Six week mortality rate (%) in all patients with suspected myocardial infarction seen by the team

Patient group	*Randomized home*	*Randomized hospital*	*Excluded from randomization*	*Total*
All patients	13	11	26	15
Patients with final diagnosis of definite/probable myocardial infarction	20	18	37	24

To resolve whether home or hospital care offered the best chance of survival for patients with myocardial infarction Mather and colleagues[4] in Bristol and the Southwest of England carried out a randomized trial using a large number of family doctors spread over a wide geographical area to enter patients and to allocate them to their treatment groups Unhappily only 24 per cent of the patients were able to be allocated randomly the remainder being electively admitted to hospital or left at home The results of this trial were dismissed by the British Joint Working Party because there were defects in its design many patients were seen late after the onset of their symptoms and there was a small and ill-defined minority of the patients who were randomised Other observers concluded that the results of the trial may well be applicable to a large proportion of patients having a heart attack at home but the paper falls tantalisingly short of proof

In Nottingham England we have recently concluded a randomized trial using a different basis for entry and allocation [5] We sent a hospital based team consisting of a junior doctor and a CCU trained nurse to patients homes in response to calls from general practitioners about patients with suspected myocardial infarction The team made an initial working diagnosis provided emergency treatment excluded unsuitable patients on predetermined grounds and observed the remainder of the patients in the home for a total of 2 hours They then randomly allocated them to home or hospital management Evidence for the diagnosis of myocardial infarction was collected according to a set plan in both groups and mortality was assessed at 6 weeks

Results

Five hundred calls were received by the team in 4 years, 349 patients were suspected of having myocardial infarction by the team on the history physical findings and ECG Of these 85 (24 per cent) were excluded on medical or social grounds the remainder 264 (76 per cent) being randomized There was no significant difference between the random groups in any of the characteristics measured including the numbers of patients requesting and receiving help at specified intervals after the onset of symptoms (by 1 hour 40 per cent of patients had called for help and by 2 hours 60 per cent had called) Myocardial infarction was proven in 79 (60 per cent) of the random home patients and in 71 (54 per cent) of the random hospital patients Twenty six patients initially randomized to the home group subsequently required hospital admission within the 6-week period the commonest reason for admission being failure to control pain at home These patients for whom home care failed were nevertheless retained in their original group for analysis The 6-week mortality rate in all patients in whom myocardial infarction was suspected is shown in Table 1 There was no significant difference in outcome between the two random groups while the mortality rate of the excluded group was considerably higher than that of the combined random groups

Discussion

Our study shows that a hospital based team responding to calls from general practitioners can identify a group of patients with suspected myocardial infarction whose subsequent prognosis is not improved by hospital admission The criteria which the team used (history physical examination and initial ECG) are available to most general practitioners and although further information (cardiac enzymes and serial ECG tracings) enables a patient with suspected infarction to be labelled retrospectively with greater confidence this information cannot be available to help a doctor to make management decisions at his first contact with the patient

In our study the team provided Coronary Care in the patient s home for two hours but it seems unlikely that this had any great influence on our results The team s main function in the study was to collect data and to ensure that

suitable patients were randomly allocated to home or hospital groups according to the study protocol The team s most important clinical role was to ensure adequate pain relief but this could equally well have been done by the patient s general practitioner Although the equipment carried by the team was important in that during a four year period eight patients were initially successfully resuscitated from cardiac arrest only three of these survived six weeks the eight patients were not included in the randomized study and therefore did not influence its results

We have therefore demonstrated that except for patients with complicated myocardial infarction or poor home circumstances hospital care confers no significant benefit in terms of six week mortality over care at home by a general practitioner We used only simple criteria to identify complicated patients and these criteria could be used equally well by general practitioners as by a hospital team Whether hospital admission helped the complicated patients was not clear but more important was our finding that 76 per cent of the patients seen by the team were suitable for care at home

Our findings support those who argue that hospital admission and the wholesale provision of CCU s is unlikely to alter community mortality rate[3] unless patients with myocardial infarction can be persuaded to call for help as soon as their chest pain develops and at a time when the risk of ventricular fibrillation is high By the time our patients decided for themselves that their pain could no longer be ignored and called for help from their family doctor hospital admission did not materially affect their outcome

We conclude that the provision of hospital based coronary care facilities will not influence community mortality rate in patients who develop chest pain and who follow the normal pattern of delaying their call for help Encouraging patients to report their chest pain at an earlier stage might influence outcome but it is likely that community mortality rate will only be significantly affected by reducing the death rate in patients for whom unheralded ventricular fibrillation is the first event Cobb and colleagues[9] have shown that the general public can be trained in cardiopulmonary resuscitation so that skilled bystanders will be available when people collapse with ventricular fibrillation or asystole in the street at work or at home

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Plasma catecholamines in acute myocardial infarction

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Reports of plasma catecholamine measurements in acute myocardial infraction have been relatively few Early studies[1-6] were carried out with a limited number of samples More recently Videbaeck and associates[7] measured total catecholamines at 2 hour intervals the first sample being obtained within 12 hours of the onset of myocardial infarction A consistant elevation of catecholamines was found and values remained stable over a 48 hour study period Strange and coworkers[8] measured total catecholamines within 1 to 10 hours of onset of acute chest pain and found a stable elevation over a 40 hour period Vetter and colleagues[9] reported catecholamine elevation within 1 hour of acute chest pain onset and measurements at hourly intervals for 5 hours showed no pattern of change

The recent development of an accurate and sensitive method[10] requiring small volumes of blood has permitted sufficient serial sampling to describe with greater precision the changes in circulating catecholamine levels occurring within the first 48 hours after the onset of acute chest pain This study was carried out in patients admitted to the coronary care unit with acute chest pain within the preceeding 24 hours and in whom a definite diagnosis of acute myocardial infarction was established

Materials and methods

Twenty three men and three women with an average age of 57 ± 2 years (ranging from 41 to 78 years) were studied There were eight cases of anterior or anterolateral infarction and 18 cases of inferior or posteroinferior infarction Zero time was determined by the onset of acute prolonged chest pain (Fig 1) and not by the appearance of ECG changes or the elevation of serum enzymes Except for two patients whose onset was actually witnessed during monitoring this timing is necessarily subjective and may have a large factor of error The first blood sample from an antecubital vein was drawn upon admission to the coronary care unit Total CPK activity was measured on blood drawn for the catecholamine determinations Blood pressure and heart rate values were recorded at the time of each blood sampling The ECG was monitored continuously on magnetic tape for the first 16 hours after admission and intermittently thereafter at hourly intervals SGOT levels were determined upon admission and twice more within the following 48 hours Patients initially received oral diazepam for sedation and demerol intramuscularly for pain Intra

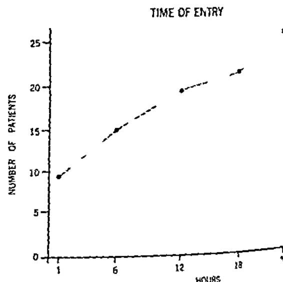


Fig 1 Cumulative curve of entry of patients into the study according to the time lapse since onset of acute chest pain

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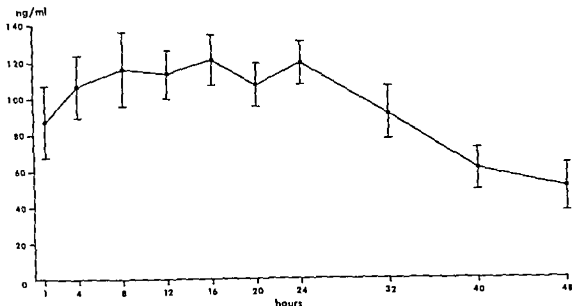


Fig 2 Mean levels ±S E of plasma catecholamines in 96 patients related to time of onset of acute chest pain

venous lidocaine was administered when ventricular arrhythmias were detected

Patients treated only with intravenous lidocaine oral diazepam or demerol administered intramuscularly were included Patients receiving other medication were not part of this study Patients with clinical manifestations of heart failure or cardiogenic shock were excluded No dietary control was carried out Acute myocardial infarction was subsequently proven in all patients both electrocardiographically and by elevated CPK and SGOT elevation 100% or more above control values Serum catecholamine levels were determined using the radiometric enzymatic microtechnique of Coyle and Henry [1] as modified by de Champlain and associates [8] for serum determinations Blood samples collected without anticoagulant at 0° C were centrifuged without delay and determinations were carried out in duplicate on the serum Normal values for plasma catecholamines obtained in 15 normotensive subjects averaged 0 218 ng /ml These values were reported elsewhere and it was pointed out that age or sex did not appear to change catecholamine values

Results

Mean catecholamine values Mean plasma catecholamine values were related to time of onset of acute chest pain which preceded admission As shown in Fig 2 circulating catecholamine levels remained elevated during the first day but these levels gradually decreased during the second 24 hours

Enzyme levels The corresponding values for serum CPK are given in Fig 3 The rise in enzyme levels occurred later than that for catecholamines and reached a plateau after 16 hours Because maximum catecholamine and CPK values did not occur simultaneously in individual patients there was no correlation between catecholamines and CPK values from the same blood sample The relationships however between peak CPK as well as peak SGOT values and peak catecholamine levels were significant This is shown in Fig 4

Heart rate and blood pressure Average heart rate and blood pressure values were initially elevated and gradually declined thereafter A significant correlation between heart rate and circulating catecholamine levels could be found as shown in Fig 5 The correlation between diastolic and systolic blood pressures and catecholamine levels was not significant Blood pressure levels and catecholamine values were found to be significantly higher when patients presented a heart rate above 100 (Fig 6) Patients with sinus bradycardia (HR < 60/minute) tended to have

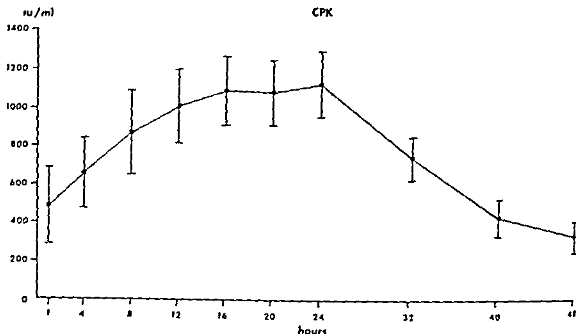


Fig 3 Mean levels ±S E of plasma CPK in 26 patients related to time of onset of acute chest pain

lower catecholamine levels and lower blood pressure values

Site of infarction Results obtained according to site of infarction are compared in Table 1 During the first 24 hour period average catecholamine values were lower but not significantly so in cases of inferior or posterior infarction During the second 24 hour period average catecholamine levels remained elevated in anterior and/or lateral infarction cases but decreased significantly ($p < 0.001$) in patients with inferior and/or posterior necrosis Average CPK levels as well as systolic and diastolic blood pressure values were not significantly different between both groups of patients Heart rate values were consistently and significantly lower ($p < 0.01$) however in inferior or posterior infarction for both 24 hour periods

Ventricular arrhythmias The relative incidence of ventricular premature beats and of ventricular tachycardia is illustrated in Fig 7 Fifty five per cent of patients observed within 1 hour of onset of acute chest pain presented ventricular ectopic beats (> 60/hour) and/or short bouts of ventricular tachycardia (three consecutive ventricular premature contractions) Sixty per cent of the patients observed within the first 6 hours after the onset of acute chest pain presented ventricular ectopic activity with a frequency of more than one ectopic beat/minute The per cent of patients with this frequency of premature beats declined thereafter [illegible] of ventricular tachycardia were not observed in patients observed more than 12 hours after onset of chest pain No other major arrhythmias were recorded Catecholamine levels were found to be significantly higher when determined when patients were presenting ectopic ventricular activity This was true both during the first and the second 24 hour periods after onset of acute infarct (Fig 8) No difference was observed as to site of infarction

Discussion

The present observations confirm the early increase in sympathetic tone following acute myocardial infarction Previous studies on circulating catecholamine levels used less sensitive techniques and therefore the number of determinations were limited Videbaeck and associates with serial measurements every 2 hours, reported higher but stable catecholamine values over the first 48 hours Griffiths and Leung however observed a gradual fall in catecholamine values within the first 24 hours Our own results confirm as well as the more recent observations of [illegible] and colleagues [illegible] that circulating catecholamines are elevated very early after chest pain [illegible] remain initially at quite high levels without appreciable fluctuation The initial sympathetic response may be part of the general body [illegible]

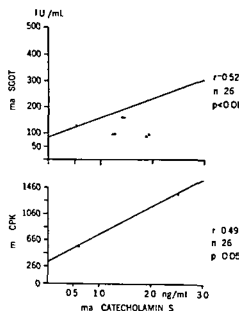


Fig 4 Relation between peak catecholamine levels and peak SGOT levels and peak CPK levels in 26 patients during 48 hours following onset of acute chest pain

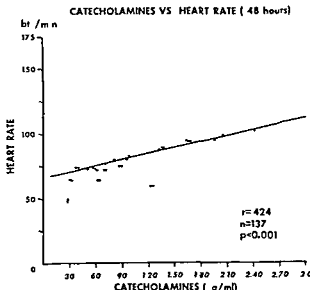


Fig 5 Heart rate at time of plasma catecholamine sampling in relation to catecholamine levels determined after onset of acute chest pain

to pain anxiety and distress Catecholamine liberation has been shown to occur from the ischemic myocardium[1] This may be a result of the effect of hypoxia on nerve endings compounded by lactate accumulation and a lowered pH Reflex sympathetic activation from the ischemic myocardium is also a distinct possibility Staszewska Barczak[1] demonstrated a reflex outpouring of catecholamines from the adrenal medulla in the early stages of myocardial infarction

Relation to blood pressure and heart rate Sinus tachycardia and elevated blood pressure are regarded as good indicators of sympathetic overactivity The importance of autonomic disturbances at the initial period of acute infarction in determining early mortality has been stressed

Fox and co workers studied the prognostic significance of an initially high systolic blood pressure in acute myocardial infarction Mortality rate the incidence of major arrhythmias and the incidence of heart failure were all greater in patients with initial systolic hypertension These patients also had higher SGOT levels suggesting more extensive infarction

A poorer prognosis has also been associated with initial sinus tachycardia In our study patients with sinus tachycardia had significantly higher catecholamine levels Sinus tachycardia is usually related to incipient heart failure and reflects the increased sympathetic drive in response to falling cardiac output or to atrial distension Patients with clinical or radiological evidence of left heart failure were deliberately excluded from our series

Relation to serum enzyme levels Previous studies carried out with measurements of urinary catecholamines suggested a relationship between catecholamine excretion and elevation of LDH SGOT levels and of white blood cell count considered indicators of the extent of myocardial damage The correlation reported here between peak catecholamine levels and peak CPK and SGOT values suggest some relation between these variables Catecholamines may themselves affect enzyme liberation from the heart[1] Although the amount of enzyme liberated may reflect the extent of structural damage induced by ischemia both catecholamine and anoxia accelerate substrate utilization and therefore may act synergistically to alter cellular function

Relation to infarct size The lower levels observed in inferior posterior infarction patients may indicate a less marked sympathetic response Parasympathetic effects predominate in this type of infarction This is corroborated by the slower

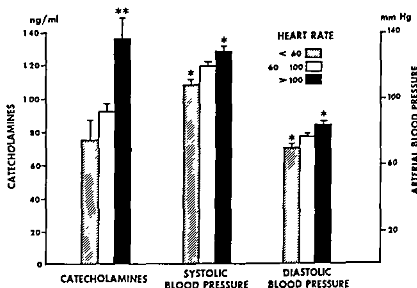


Fig 6 Catecholamine levels mean systolic blood pressure and mean diastolic pressure in patients with heart rates below 60 beats/minute between 60 and 100 beats/minute and above 100 beats/minute p < 0 05 p < 0 01

Table I

		Mean catecholamines	Mean heart rate	Mean systolic BP	Mean diastolic BP	Mean CPK
Anterior and lateral infarctions	First 24 hours	1 73 ± 49	108 ± 8	139 ± 6	86 ± [illegible]	403 1??
	Second 24 hours	1 81 ± 19	122 ± 6	125 ± 3	8? ± 5	635 + 14?
Inferior and posterior infarctions	First 24 hours	1 05 ± 10	76 ± 3	121 ± 6	[illegible]3 ± ?	635 [illegible]
	Second 24 hours	0 45 ± 07	72 ± 8	114 ± 4	73 3 ± 3	436 [illegible]

p < 0 01
p < 0 001

heart rates observed The relation between catecholamine levels and infarct site may also reflect a lesser degree of left ventricular dysfunction in posteroinferior infarcts

A recent study suggested that site of infarction is important in determining outcome of sudden death and that beta blocking agents reduce mortality in anterior or anterolateral infarction significantly probably by prevention of life threatening arrhythmias It is intriguing to speculate whether the higher catecholamine values observed in anterior infarction during both first and second 24 hour periods can be related to the beneficial effect of beta adrenergic blockage reported in the Multicenter Study

Relation to ventricular arrhythmias The increased adrenergic response in myocardial infarction has always been suspected of contributing to the occurrence of the arrhythmias of the early phase [21] Because exogenous catecholamines can experimentally cause ventricular extrasystoles or tachycardia after coronary occlusion, they are easily incriminated and invoked as causes of rhythm disturbances An increased incidence of arrhythmias has usually been observed in patients with greater urinary catecholamine excretion rates [3, 24] or with higher plasma catecholamine concentrations McDonald and coworkers found plasma catecholamine levels to be higher in patients with atrial dysrythmias and early ventricular dysrhythmias Siggers and colleagues[3] found a relationship between plasma adrenaline levels and ventricular arrhythmias Experimentally Richardson and associates were unable to establish a correlation between plasma catecholamine concentrations and the incidence and severity of ventricular arrhythmias in dogs after coronary artery ligation However

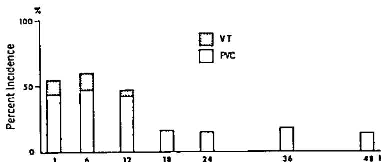


Fig 7 Relative incidence of premature ventricular contractions (PVC) and of ventricular tachycardia (VT) at various time intervals after onset of acute chest pain

Staszewska Barczak[13] using a bioassay technique related the appearance of arrhythmias to the secretion of adrenaline into the adrenal vein. The present method of catecholamine determination did not allow the separate estimation of noradrenaline and adrenaline levels. Considerable evidence points to the importance of high circulating adrenaline in acute myocardial infarction. The effects of adrenal secretion may be quite different either on metabolic effects, blood pressure, heart rate, or the occurrence of arrhythmias.

The arrhythmias observed in most patients with acute myocardial infarction are more frequent in the more severely ill patients. Hypoxemia, acidosis, and the myocardial distension which accompanies heart failure are arrhythmogenic per se and are accompanied by adrenergic stimulation. Arrhythmias themselves can possibly provoke catecholamine secretion by reducing cardiac output. The relative low incidence of ventricular ectopic activity in our series probably reflects the selection of a population of patients without obvious complications. The catecholamine values measured coincidentally while the patients presented arrhythmias were higher than when no arrhythmias were present. It is not possible to establish, however, at this point a causal relationship between the degree of catecholamine elevation and the occurrence of ventricular arrhythmia. While the present manuscript was being prepared for submission for publication, Strange and co-workers published a study quite similar in design to our own. In contrast to our observation they were unable to find any relation between increased catecholamine concentrations and the incidence of ventricular arrhythmias.

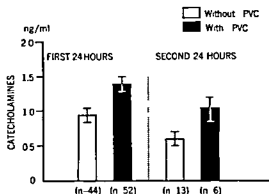


Fig 8 Catecholamine levels when premature beats or ventricular tachycardia were present at time of sampling during either the first or the second 24 hour period after onset of acute chest pain. $p < 0.05$ $p < 0.01$

Summary

Plasma catecholamine levels were determined in 26 cases of uncomplicated myocardial infarction within 24 hours of onset of acute chest pain. Blood samples were collected at time of entry and at 4 hour intervals during the 48 hours following admission. Average values of plasma catecholamines within 1 hour of onset of pain were 0.87 ng/ml ± 0.21 and remained elevated during the first 24 hours period. A gradual fall in catecholamine values was observed during the second 24 hour period. Catecholamines were higher in patients with sinus tachycardia and lower in patients with sinus bradycardia and were higher

in patients with anterior or anterolateral infarction. Catecholamine values were significantly higher when determined while patients presented ventricular ectopic beats or ventricular tachycardia. Sinus tachycardia, ventricular arrhythmias and elevated plasma catecholamine values may be considered indicators of pain, anxiety and/or left ventricular dysfunction without necessarily being causally related between themselves.

Our thanks to Ms. L. Bouchard and Ms. L. Farley for their technical assistance and to Ms. G. Dubé and the coronary care unit nursing staff for their cooperation.

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Relationship between extent of coronary artery disease and correlative risk factors

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Many risk factors—serum lipids hypertension sex diabetes mellitus life habits nutritional status and ethnic background—have been incriminated in the etiology of coronary atherosclerosis[1] The relative importance of each risk factor still remains uncertain

The severity of coronary atherosclerosis is best estimated from pathological specimens taken at necropsy and the degree of atherosclerosis can then be related to the relative severity of the known risk factors in the same population[2-] This method implies a clinicopathological correlation made at the time of death Coronary angiography is the only method by which it is feasible to measure accurately the degree of coronary atherosclerosis during life Comparison of the results of coronary angiography with the patient s biological and biochemical background permits accurate evaluation of the importance of each risk factor The literature on the subject is scanty and observations have been limited to a simple visual assessment of the extent of the coronary atherosclerotic process and the presence or absence of each risk factor

This is a prospective study of the correlation of coronary atherosclerosis as measured angiographically with known risk factors in individuals with angina pectoris

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Patients and methods

One hundred forty patients were studied All patients were referred for coronary angiography because of chest pain thought to be due to angina pectoris

A full history was taken and a complete physical examination was made The following were noted duration of residence in Israel duration of clinical history of angina pectoris number of previous myocardial infarctions smoking habits and family history of atherosclerotic heart disease Patients were regarded as hypertensive if the resting blood pressure was above 150 mm Hg systolic and/or 90 mm Hg diastolic Obesity was evaluated from the patient s weight related to his height according to the method described by Koh and Sask[1] Patients who had not smoked for the ten years previous to the study were considered as non smokers

The population of Israel has a heterogeneous background and 70% were born in other countries Patients were classified according to their ethnic origin where ethnic origin refers to country of birth and environmental life style Ashkenazi Jews are of European origin (Germany Poland Russia Hungary Roumania England and the U S A) Sephardic Jews come from the Mediterranean littoral where they settled in the wake of the seventh century Moslem conquest from Iran and other Middle Eastern countries Yemenite Jews were born in Aden

Patients were admitted to the hospital for evaluation Drug therapy was stopped on the night before angiography None of the patients received lipid lowering drugs or anticoagulants

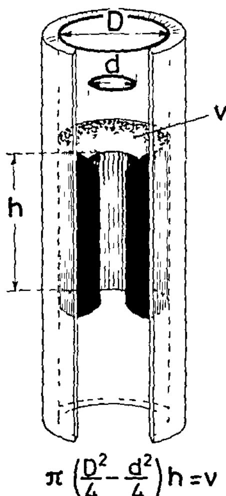


Fig 1 Schematic illustration of the calculation used for measurement of the atheromatous volume D = internal diameter of the healthy coronary artery d = internal diameter of the arterial diseased segment h = length of atheromatous lesion v = volume of atheroma

Venous blood was drawn in the fasting state Blood glucose levels were determined by the auto analyzer technique Patients were considered diabetic if the patient had clinical diabetes mellitus if the fasting blood glucose level was above 120 mg % or if this had been elevated previously The level in the blood of triglycerides cholesterol and lipoproteins were determined as previously described These lipid and lipoprotein levels were compared to a group of normal Jerusalem subjects aged 50 to 60 years

Coronary arteriography was performed by the Judkins technique using a General Electric angiographic system with a 4½ inch image intensifier Multiple injections of contrast medium were made into each coronary artery and were filmed in several oblique projections Angiograms were evaluated by at least two observers

Three methods of angiographic assessment were used to evaluate the severity of coronary artery disease

1 *The total number* of atheromatous lesions in the coronary arteries were added irrespective of the severity of narrowing of each artery

2 *Coronary atherosclerotic score* The severity of each lesion was estimated and given a score in which a score of 1 was given to a lesion which produced a maximum obstruction of 10 to 50% of the lumen of the artery in any projection a score of 2 was assigned for 50 to 70% obstruction a 3 was given for 75 to 90% obstruction and a score of 4 was assigned for an obstruction of more than 90% of the arterial lumen The total score was then determined for each patient

3 Estimation of the *total volume of atheromatous material* The length and internal diameter of the apparently normal coronary artery segment was measured The length and thickness of each atheromatous lesion was then measured and the volume of atheroma was calculated (Fig 1) The volume of each atheromatous lesion was calculated using a method of concentric cylinders and the total volume of atheromatous material was determined for each patient

Statistical analysis of the interrelationship between the different factors was made by multiple regression analysis using a linear additive model The general form of the multiple regression is

$$Y_i = A + B\ X_1 + \qquad + B\ X_k$$

where Y_i represents the estimated value of Y A is the Y intercept X_1 X_k are the independent variables and B_1 B are the regression coefficients

The coefficients A and B_i are selected so that the sum of the squared residuals $(Y - Y_i)$ is minimal Selection of the optimal coefficients A and B using the least square criterion implies that any other values for A and B_i would yield a large $(Y - Y_i)$ Statistical analysis was carried out with the aid of the CDC 6400 computer at the Hebrew University Computer center

The different correlative factors were examined in what appeared to be the most logical descending order of importance The order was varied until the statistically most significant order of correlative importance was obtained

Results

One hundred and forty patients were studied Of great interest is the fact that 33 had normal

Table I Clinical data

Correlative factors	*No of patients*	*Correlative factors*	*Mean ± S.D*
Males	109	Age	52 9 ± 9 1 years
Females	31	Duration of overt coronary artery disease	4 4 ± 4.3 years
Hypertension	43	Number of myocardial infarctions	0 6 ± 0 7
Diabetes mellitus	26	Number of cigarettes per day	16 1 + 18
Previous myocardial infractions	7?	Obesity % of ideal body weight	115 5 ± 14%
Family history of atherosclerotic disease	73	Duration of residence in Israel	3? 1 ± 15 years
Origin			
Ashkenazi	94		
Sephardi	4?		
Yemenite	4		
Smokers	76		

Table II Lipid analysis

		Healthy population	*Patients with CAD*	
Cholesterol mg /dl	males	200 2 ± 38.2 (514)†	213 0 ± 40 7 (90)†	$p < 0\,005$
	females	211 4 ± 40 4 (311)	237 0 ± 7? 8 (18)	$p < 0\,00?$
Triglycerides mg /dl	males	147 3 ± 8? (514)	172 ? ± 88 (90)	$p < 0\,01$
	females	128 5 ± ?6 7 (311)	140 3 ± 48 7 (18)	NS
H D L cholesterol mg /dl	males	41 7 ± 11 (404)	35 4 ± 15 5 (86)	$p < 0\,00?$
	females	52 9 ± 14 1 (308)	43 9 ± 13 7 (18)	$p < 0\,01$

Healthy population consists of a group of male and female residents of Jerusalem aged ?0 to 60 years without clinical evidence of coronary artery disease The group of patients with CAD consists of the 109 patients (90 males and 18 females) with angina pectoris and angiographically documented coronary atherosclerosis

†Number in parentheses are number of subjects.

coronary arteriograms The clinical and biochemical profile of the entire group are summarized in Table I Table II compares the lipid levels in the patients with angiographically proven coronary artery disease and in the age and sex matched control population Patients with coronary artery disease had higher levels of serum cholesterol ($p < 0\,005$) and triglycerides ($p < 0\,01$) but a lower level of high density lipoprotein cholesterol than the control subjects ($p < 0\,005$)

The angiographic results and the correlation between the three methods of measuring the extent of atheroma are summarized in Table III There was an excellent cross correlation between all three methods of assessing angiographically the severity of coronary artery atheroma between the volume of atheroma and the coronary score ($r = 0\,84$) between the number of lesions and the coronary score ($r = 0\,92$) and between the atheromatous volume and the number of lesions ($r = 0\,77$) In the statistical analysis there was no significant difference

Table III Angiographic indices of coronary artery atheroma

	Mean ± S.D
1 Coronary atheroma score	11 4 ± 10 1
2 Volume of atheromatous material	13 6 ± 14 4 mm
3 Total number of atheromatous lesions	4.5 ± 3 9

Angiographic indices of coronary artery atheroma were determined as described in Methods section The correlation coefficients (R) between the different methods for the assessment of coronary atheroma were as follows

(1 + 2) = 0.84 r (1 + 3) = 0.9?, r (2 + 3) = 0 77

between the relationship of correlative risk factors and the severity of atheroma where atheromatous volume number of lesions or coronary score were used as the dependent variable Since the coronary score is simple to measure we elected to use this as the angiographic yardstick and have therefore related the risk factors to the coronary score

Table IV Multivariate statistical analysis Relationship of coronary artery score to pathogenetic factors

	B	*Standard error (B)*	r^2 *change*	*Significance* $p \leq$
Duration of overt C A D (years)	0 656	0 193	0 209	0 001
Male sex	7 992	2 082	0 073	0 001
Number of previous myocardial infarctions	3 852	1 132	0 061	0 001
Cholesterol (mg %)	0 076	0 019	0 035	0 001
Diabetes mellitus[b]	4 394	1 975	0 022	0 028
Number of cigarettes smoked per day	0 000[illegible]	0 04[illegible]	0 017	0 991
Duration of residence in Israel (years)	0 0 6	0 0[illegible]	0 006	0 269
HDL cholesterol (mg %)	0 006	0 052	0 005	0 911
Relative body weight (%)	0 08[illegible]	0 053	0 004	0 111
Hypertension[a]	2 121	1 618	0 003	0 192
Family history	1 96[illegible]	1 5[illegible]	0 001	0 207
Serum triglycerides (mg %)	0 005	0 01	0 001	0 600

B values are derived from equation (1) and are the coefficient of each variable Variables marked by *a* are assessed in absolute values i e years of duration of CAD number of previous myocardial infarction mg % cholesterol etc The value of 1 is assigned for a yes situation and 0 for no situation to variables marked by *b* i e male 1 and female 0 diabetes mellitus 1 and no diabetes mellitus 0 etc

Table IV summarizes the relationship of each correlative factor to the coronary score and shows the statistical importance of each variable in the multiple regression equation (B value Table IV) It also shows the contribution of each variable to the total prediction of the coronary score (r^2 changes Table IV) Seventeen different variables were analyzed five were found to be non related to the extent of coronary atherosclerosis and were removed from the multiple regression analysis These five variables were age country of emigration ethnic origin VLDL and LDL cholesterol Of the 12 variables which remained and which formed 43% of the statistical prediction only five were significant and these together accounted for 93% of the predictive value of this subset The most important contributory factor was duration of clinical disease The other important significant correlative factors were male sex number of previous myocardial infarctions elevated serum cholesterol and diabetes mellitus In the multivariate analysis cigarette smoking obesity hypertension a family history of atherosclerosis and elevated serum triglycerides had a positive influence but this was not significant statistically

Discussion

Coronary atherosclerosis is a progressive condition whose precise etiology and pathogenesis remain uncertain It appears that cholesterol and other lipids are deposited in the intima of the coronary arteries a process which progresses with age The rate of deposition however is governed by different hereditary and environmental factors Each patient may have his own rate of lipid deposition and this may subsequently be influenced by modification of his normal environment or living habits or by therapeutic intervention [1]

Many previous necropsy studies have examined large population groups by methods which are only epidemiologically reliable when applied to the deceased [3,6,11,14] Other studies related clinical episodes of coronary artery disease to changes in the electrocardiogram These studies relating to clinical events have taken into account possible errors in clinical or electrocardiographic diagnosis [17,19] There are few reports of the relationship between coronary atheroma studied at angiography and underlying pathogenetic mechanisms [7,11]

The present study examines the precise degree of coronary artery disease and relates it to underlying pathogenetic causes It contains a selected clinical group of patients who presented with chest pain or angina pectoris thought to be of sufficient severity to justify consideration of the patient for surgical treatment it was a group of patients who developed important clinical angina pectoris The study thus has no epidemiological implications nonetheless it does permit analysis of the relationship between the extent of the coronary atherosclerotic process in life and possible pathogenetic factors

There are many methods of assessing the degree of coronary atheroma at angiography Most workers have relied on estimating the degree of disease in each major coronary artery and have classified their patients according to the number of arteries affected [1] Others have assessed the extent and severity of each lesion in the coronary arteries and have used the total

score by assigning points to the severity of each lesion [9, 1]

There are many problems in assessing the extent of atheroma from the coronary arteriogram [6] The accuracy of investigation depends on the quality of coronary angiography with poor resolution angiography it is common to underestimate the degree of atheroma and a small plaque may not be apparent or easily recognized Similarly angiograms made in one or two projections only may not demonstrate significant lesions We have used a 4½ inch image intensifier and an overframing lens to produce optical magnification and used sensitive fine grain film in order to obtain maximum photographic resolution It is doubtful whether we underestimated significant lesions *Another cause of error occurs when there* is total obstruction of an artery a coronary artery may be obstructed completely and have no distal flow in these circumstances it is not possible to assess the degree of atheroma in the distal artery Further errors may be due to inter observer variability in interpretation [21] All our angiograms were assessed independently by at least two observers

We attempted therefore to quantitate the degree of atheroma precisely by measuring the exact volume of atheroma from the angiogram A coronary artery is a tapering cylinder [22] atheroma protrudes into the lumen and produces luminal distortion so that measuring concentric cylinders can be used to evaluate the volume of atheroma Accurate measurements of coronary artery volume are time consuming but these are related statistically to the total number of atheromatous lesions and to a coronary score which takes into account the number of lesions and the degree of obstruction produced by each lesion We elected to use the score since this was simple to assess and appeared to have great clinical value

A multiple regression logistic model permits identification of each important correlative risk factor and allows assessment of the contribution of each factor to the over all pathological picture [6, 3] Single factor regression analysis examines only one correlative risk factor at a time and ignores the contribution of others Thus two factors which are interdependent one on the other may both appear significant in single factor regression analysis but multiple regression analysis will determine which is of greater importance

Our multiple regression analysis has shown five highly significant factors related to the severity of the atheromatous process duration of overt clinical disease number of previous episodes of myocardial infarction male sex elevation of serum cholesterol and diabetes mellitus The importance of the first two factors is self evident If the disease is considered to be progressive and progresses at a specific rate in a given patient [1] then a longer history and more episodes of myocardial infarction must be associated with more severe atheroma When the influence of these two major factors is removed serum cholesterol and the presence of diabetes mellitus become the most important significant correlative factors The level of serum cholesterol *appeared to be the major pathogenetic factor* The relationship is so clear that one may question whether it is necessary to undertake extensive lipoprotein studies in individual patients Diabetes mellitus is another major independent pathogenetic factor and this is in keeping with the findings of other studies We did not separate patients with juvenile and adult onset diabetes mellitus or measure the duration of the diabetes or assess its severity since the number of patients was too small The reason for the masculine preponderance is probably related to the age distribution of patients selected This was a specific group of younger patients selected as potential surgical candidates Coronary artery atheroma below age 50 is predominantly a male disease since premenopausal women have an endocrinal protective mechanism The sex discrepancy diminishes as age increases [3]

Less significant but positive factors were cigarette smoking obesity hypertension a family history of atherosclerosis and elevated serum triglycerides The mechanism whereby cigarette smoking causes atheroma is still an enigma Our conclusions suggest that cigarette smoking is a factor in the development of atherosclerotic disease It may also trigger an arterial occlusion or in the case of sudden death produce an arrhythmia in subjects who already have myocardial ischemia from atherosclerotic coronary artery disease [1] The role of obesity is less clear but again the directional change is evident and this may be related to the higher lipid load Elevated serum triglycerides exert a positive but much smaller pathogenetic role There was no significant relationship to LDL or VLDL plasma

cholesterol levels above that of plasma cholesterol

Age and ethnic origin did not appear to play a significant role This probably reflects the process of the patients selection most of the patients had clinically important coronary artery disease Thus both younger and older subjects were studied when the degree of coronary artery narrowing was sufficient to cause severe angina pectoris Similarly Sephardi patients born in North Africa or Asia where the incidence of coronary artery disease is known to be lower than in Ashkenazi patients born in Eastern Europe Israel and the U S A [4] *formed only a small fraction of the group* under study The few patients from these ethnic environments who did enter the study usually had other risk factors which induced coronary disease

The lack of negative correlation with HDL cholesterol levels is surprising although the patients with coronary artery disease had lower levels of HDL than the age matched control subjects Recent studies have shown that patients with elevated HDL have a lower incidence of coronary artery disease [5] However in the present study we have attempted to correlate HDL cholesterol levels not with the presence of coronary atherosclerosis but rather with the severity of the disease It is then possible that HDL cholesterol levels—as well as other variables—may be detrimental to the development of the atherosclerotic disease but *not to the extent and rate of* progression of the process More studies however are needed to confirm or rule out this view

Summary

An analysis was made of correlative factors which might be related to the angiographically measured extent of coronary artery disease in 140 patients All patients presented with clinically important chest pain Thirty three had a normal coronary arteriogram The extent of the atheromatous process was measured precisely at angiography by three different techniques A coronary score based on the percentage of luminal narrowing was found to be best suited for the analysis The most important contributory factors to the severity of atherosclerosis were duration of clinical history number of previous myocardial infarctions and male sex but more specifically elevation of serum cholesterol and diabetes mellitus Cigarette smoking obesity hypertension a family history of atherosclerosis and elevated serum triglycerides had a positive influence but this was not statistically significant

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Progression of mild mitral stenosis and incidence of restenosis after open commissurotomy. A study using echocardiography

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Edler[1] demonstrated the value of *M mode echocardiography* in diagnosing mitral stenosis and quantitating *its degree of obstruction*. In addition, this *technique is of help* in following the natural *history of mitral* stenosis and in the postoperative evaluation of *patients who have* undergone commissurotomy.[3] In particular, the diastolic *closing velocity* (E F slope), the amplitude (C E),[6] *of the anterior mitral leaflet*, the movement of the *posterior leaflet*, as well as certain indices such as the *mitral valve closure* index (DE/MAIC) were shown to be useful parameters. *Hemodynamic follow up* studies have revealed that the progression of mitral stenosis and restenosis *after operation* is a gradual process which occurs over several years. However, little information is available on the rate of progression in asymptomatic or mildly symptomatic patients. The purpose of the present investigation was to assess echocardiographically the rate of progression of mitral stenosis and the incidence of restenosis after commissurotomy.

Patients and methods

Patients. In 13 patients with mitral stenosis (*three men and 10* women, mean age 44.0 years) two echocardiograms separated by 37.3 ± 5.9 months were obtained. Eleven patients were in normal sinus rhythm and two patients had atrial fibrillation. All patients were in NYHA Class I and II. In 11 patients surgical correction was not warranted, whereas two patients with atrial fibrillation refused operation.

In 21 asymptomatic patients (one man and 20 women with a mean age of 45.6 years) an echocardiogram was obtained 3 to 4 weeks after open commissurotomy and a follow up recording was made after 48.2 ± 6.4 months. Fifteen patients were in normal sinus rhythm and six patients had atrial fibrillation.

Methods. The first follow up studies were made partly with a Unirad Sonograf Model 150 Scanner, partly with a Picker Ultrasonoscope Model 103 and a Picker Echoview System 80 C, whereas all the final studies were done using the Picker Echoview System 80 C. For the assessment of the degree of mitral stenosis we used the following measurements (Fig. 1).

1. The diastolic closing velocity of the anterior mitral leaflet (E F slope [mm/sec]).
2. The opening amplitude of the anterior mitral leaflet (D E [mm]).
3. The amplitude of the anterior mitral leaflet at the onset of left ventricular isovolumic contraction (MAIC) which coincides with the R wave of the electrocardiogram.
4. Finally, the DE/MAIC index was calculated.

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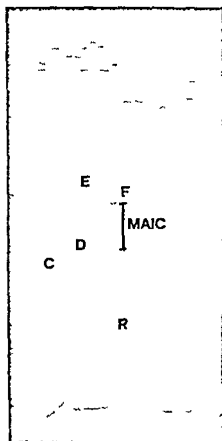


Fig 1 Echocardiogram of the anterior and posterior leaflets of the mitral valve in mitral stenosis *D E* Opening amplitude of the anterior mitral leaflet *E F* Diastolic closing velocity of the anterior mitral leaflet *MAIC* Amplitude of the anterior mitral leaflet at the beginning of the isovolumic contraction

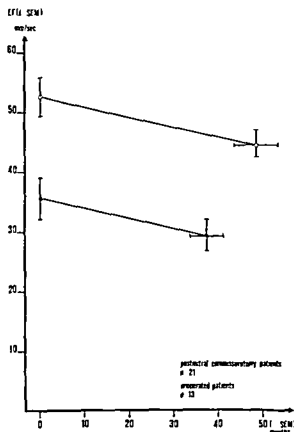


Fig 2 Diastolic closing velocity (E-F slope) in mitral stenosis *(closed circles)* and after open commissurotomy *(open squares)* Δ t represents time elasped between the two recordings

Results

In patients with *mitral stenosis* there was a significant decrease of the E F slope from 35.7 ± 3.5 to 29.5 ± 2.7 ($p < 0.0005$) over a period of 37 months (Fig 2) The mitral valve opening amplitude (D E) decreased from 18.0 ± 0.6 to 14.9 ± 0.5 ($p < 0.0005$) and the amplitude of the mitral echo at the beginning of isovolumic contraction (MAIC) decreased from 11.7 ± 0.5 to 9.9 ± 0.6 ($p < 0.005$) The index DE/MAIC was not significantly changed (1.6 ± 0.1 vs 1.5 ± 0.1) (Table I Fig 3)

Patients who had undergone open *mitral commissurotomy* showed a slowing of the diastolic closing velocity from 52.6 ± 3.2 to 44.8 ± 2.3 ($p < 0.005$) over a period of 48 months (Fig 2) The D E amplitude decreased from 18.2 ± 0.5 to 16.6 ± 0.6 ($p < 0.0005$) and MAIC decreased from 11.2 ± 0.5 to 10.4 ± 0.4 ($p < 0.005$) In this group of patients the index DE/MAIC changed from 1.7 ± 0.04 to 1.5 ± 0.05 ($p < 0.0025$) (Table II Fig 3)

There was no significant correlation between the parameters of mitral stenosis and the time elapsed between the two recordings both in patients with mitral stenosis and in patients after commissurotomy (Tables III and IV) In all patients the posterior mitral leaflet moved in the pattern characteristic of mitral stenosis

Discussion

Progression of obstruction in patients with mitral stenosis This investigation deals with 11 patients who were in normal sinus rhythm and who had little or no symptoms at the initial study and two patients with atrial fibrillation who refused operation Of all the initially asymptomatic patients with mitral stenosis seen at our institution no one failed to have a second echo

Table I Echocardiographic data of 13 patients with mitral stenosis obtained after an interval of 37 3 ± 5 2 months (2)

Patient	Sex	Age (years)	Rhythm	Δ t (months)	E F1 (mm / sec)	E F2 (mm / sec)	Δ E F (mm / sec)	D E1 (mm)	D E2 (mm)	MAIC 1 (mm)	MAIC 2 (mm)	DE/ MAIC 1	DE/ MAIC 2	Δ DE/ MAIC
B L	F	46	NSR	25	52	46	− 6	20	16	11	9	1.8	1.8	0
C C	F	50	NSR	19	26	20	− 6	17	13	11	9	1 5	1 4	−0 1
D G	F	45	NSR	37	42	35	− 7	18	14	10	9	1.8	1 6	−0.2
G R	F	66	NSR	32	22	22	0	20	17	16	15	1 3	1 1	−0.2
L G	F	38	NSR	62	32	28	− 4	14	12	11	10	1.3	1.2	−0.1
M C	F	46	NSR	16	34	33	− 1	16	16	−	−	−	−	−
S M	F	57	NSR	63	50	35	−15	22	12	12	8	1.8	1.5	−0.3
S G	F	41	NSR	63	59	43	−16	19	15	12	9	1 6	1 [illegible]	+0 1
T T	F	31	NSR	43	33	30	− 3	16	16	−	−	−	−	−
T L	M	42	NSR	22	35	25	−10	16	15	12	11	1 3	1 4	+0 1
Q K	F	28	NSR	35	37	33	− 4	20	18	−	−	−	−	−
F G	M	35	AF	11	12	10	− 2	18	16	12	10	1.5	1 6	+0 1
F L	M	48	AF	57	30	24	− 6	18	14	10	9	1 8	1 6	−0.2
Mean		44 1		37.3	35 7	29 5	− 6 15	18 0	14 9	11 7	9 9	1 6	1.5	−0 08
SEM		2 9		5.2	3 5	2 7	1 4	0 6	0 5	0 5	0 6	0 1	0 1	0 05
p <						0 0005			0 0005	0 0005			NS	
2 SD							9 86							0.30

NSR = normal sinus rhythm AF = atrial fibrillation Δ t = time elapsed between initial recording (1) and follow up tracing (2)
No simultaneous ECG available

Table II Echocardiographic data of 21 patients obtained immediately following commissurotomy (1) and after 48 2 ± 6 4 months (2)

Patient	Sex	Age (years)	Rhythm	Δ t (months)	E F1 (mm / sec)	E F2 (mm / sec)	Δ E F (mm / sec)	D E1 (mm)	D E2 (mm)	MAIC 1 (mm)	MAIC 2 (mm)	DE/ MAIC 1	DE/ MAIC 2	Δ DE/ MAIC
A M	F	40	NSR	13	41	41	0	16	15	10	10	1 6	1.5	−0 1
C F	F	39	NSR	10	54	52	− 2	18	18	−	−	−	−	−
F E	F	41	NSR	88	35	32	− 3	15	13	10	9	1.5	1 4	−0.1
G R	F	43	NSR	86	50	43	− 7	22	20	16	14	1 4	1 4	0
G D	F	50	NSR	59	51	40	−11	17	12	10	8	1 7	1.5	−0.2
H A	F	49	NSR	50	37	28	− 9	16	16	−	−	−	−	−
H A	F	35	NSR	37	62	43	−19	20	18	10	10	2 0	1.8	−0.2
K L	F	45	NSR	8	53	46	− 7	18	17	−	−	−	−	−
N R	M	38	NSR	60	[illegible]	55	−20	19	18	12	11	1 6	1 6	0
R L	F	41	NSR	35	50	46	− 4	19	14	11	10	1 7	1 4	−0.3
R C	F	46	NSR	6	25	24	− 1	15	14	−	−	−	−	−
R W	F	39	NSR	80	54	54	0	20	16	12	10	1 7	1 6	−0 1
S M	F	49	NSR	[illegible]8	82	62	−[illegible]0	1[illegible]	17	10	10	1 7	1 [illegible]	0
Y K	F	41	NSR	[illegible]4	[illegible]6	58	−18	22	20	1[illegible]	12	1 8	1 [illegible]	−0 1
W T	F	49	NSR	48	36	32	− 4	18	18	−	−	−	−	−
D W	F	41	AF	9[illegible]	44	40	− 4	18	18	10	10	1.8	1.8	0
D A	F	[illegible]4	AF	34	58	[illegible]0	− 8	1[illegible]	13	10	10	1.5	1.3	−0.2
R A	F	[illegible]	AF	3	60	57	− 3	20	20	−	−	−	−	−
S E	F	[illegible]	AF	44	67	55	−12	20	20	−	−	−	−	−
S L	F	46	AF	1	43	34	− 9	19	14	12	11	1 7	1.3	−0 4
L W	F	44	AF		5[illegible]	48	− 4	19	18	−	−	−	−	−
Mean		4[illegible]		[illegible]	52 6	44.8	− 7.86	18 2	16 6	11.2	10 4	1 [illegible]	1.5	−0.13
SEM		1 8		[illegible]	3 2	2 3	1 43	0.5	0 6	0 5	0 4	0 04	0 05	0 04
p <						0 0005			0 0005	0 005			0 0025	0.[illegible]
2 SD							13 15							

For abbreviations see Table I

Table III Correlation between the change of echocardiographic parameters and interval between two measurements (Δ t) in patients with mitral stenosis

	Δ EF	Δ DE	Δ MAIC	Δ DE/MAIC
r	−0 55	−0 48	−0.30	−0 4?
p	>0 05	>0 05		
	<0 1	<0 1	>0 1	>0 1

Table IV Correlation between the change of echocardiographic parameters and interval between two measurements (Δ t) in patients following open commissurotomy

	Δ EF	Δ DE	Δ MAIC	Δ DE/MAIC
r	−0 29	−0 23	−0 33	−0 40
p	>0 1	>0 1	>0 1	>0 1

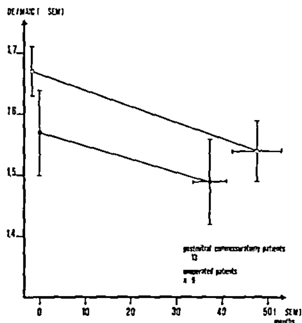


Fig 3 DE/MAIC index in mitral stenosis *(closed circles)* and after open commissurotomy *(open squares)* Δ t represents time elapsed between the two recordings

cardiogram due to intervening surgery However it is clear that our group represents a selected sample of the various stages of this disease since surgery cannot be withheld from the more severe cases We observed a slight though clinically inapparent progression of mitral stenosis which did however not correlate significantly with the interval between the two examinations (r = −0 55 p < 0 1 Table III) Three of 13 patients (23%) showed a significant progression defined as a slowing of the E F slope and/or a diminution of the DE/MAIC index of more than 2 SD (Δ E F and Δ DE/MAIC respectively) Dubin and colleagues in a hemodynamic follow up study of a similar group of patients with mitral stenosis found progression in 18 of 42 (43%) non operated patients over 3 7 years They indicate that this ratio is probably too high a statement which is corroborated by our findings In a study of the natural history of mitral stenosis Selzer and Cohn found that the disease may show very slow progression in some patients and may worsen rapidly in others depending on the degree of involvement of the mitral apparatus by the rheumatic process As shown in our study and by Dubin and colleagues mild mitral stenosis is associated with only minimal progression over 3 years This progression is just detectable by echocardiography

The group of patients after commissurotomy again represents a selected sample since this type of surgery was performed only on valves without calcification and in the absence of regurgitation In addition it must be noted that all patients were asymptomatic postoperatively Consequently it is not surprising that the incidence of restenosis in our patients (24%) is below that reported by others [11] Ellis and Harken [3] had to reoperate on 20% of their patients with mitral valvuloplasty after 9 years It is conceivable that this group of patients and those of our patients in whom restenosis was demonstrable are identical and that reoperation will eventually be required Higgs and co workers [9] found a somewhat lower incidence of restenosis (11%) after 8 3 years

In conclusion we feel that follow up examinations of patients with mild mitral stenosis and asymptomatic patients after mitral commissurotomy need to be repeated only every 3 years approximately

Summary

Thirteen patients with mild mitral stenosis and 21 asymptomatic patients after commissurotomy were studied by echocardiography in order to assess the rate of progression of mitral stenosis and the incidence of restenosis after successful open mitral commissurotomy In the gr

Table I Echocardiographic data of 13 patients with mitral stenosis obtained after an interval of 37 3 ± 5 2 months (2)

Patient	Sex	Age (years)	Rhythm	Δ t (months)	E F1 (mm / sec)	E F2 (mm / sec)	Δ E F (mm / sec)	D E1 (mm)	D E2 (mm)	MAIC 1 (mm)	MAIC 2 (mm)	DE/MAIC 1	DE/MAIC 2	Δ DE/MAIC
B L	F	46	NSR	25	52	46	− 6	20	16	11	9	1.8	1.8	0
C C	F	50	NSR	19	26	20	− 6	17	13	11	9	1.5	1 4	−0 1
D C	F	45	NSR	37	42	35	− 7	18	14	10	9	1.8	1.6	−0.2
G R	F	66	NSR	32	22	22	0	20	17	16	15	1.3	1 1	−0.2
L G	F	38	NSR	62	32	28	− 4	14	12	11	10	1.3	1.2	−0 1
M C	F	46	NSR	16	34	33	− 1	16	16	–	–	–	–	–
S M	F	57	NSR	63	50	35	−15	22	12	12	8	1.8	1.[illegible]	−0.3
S G	F	41	NSR	63	[illegible]9	43	−16	19	15	12	9	1 6	1 7	+0 1
T T	F	31	NSR	43	33	30	− 3	16	16	–	–	–	–	–
T L	M	42	NSR	22	35	25	−10	16	15	12	11	1.3	1 4	+0 1
Q K	F	28	NSR	35	37	33	− 4	20	18	–	–	–	–	–
F G	M	3.	AF	11	12	10	− 2	18	16	12	10	1.5	1 6	+0 1
F L	M	48	AF	57	30	24	− 6	18	14	10	9	1 8	1 6	−0.2
Mean		44 1		37.3	3[illegible] 7	29 5	− 6 15	18 0	14.9	11 7	9.9	1 6	1.5	−0.08
SEM		2 9		5 2	3 5	2 7	1 4	0 6	0.5	0 5	0 6	0 1	0 1	0 0[illegible]
p <					0 0005			0 0005		0 0005		NS		0.30
2 SD							9 86							

NSR = normal sinus rhythm AF = atrial fibrillation Δ t = time elapsed between initial recording (1) and follow up tracing (2)
No simultaneous ECG available

Table II Echocardiographic data of 21 patients obtained immediately following commissurotomy (1) and after 48 2 ± 6 4 months (2)

Patient	Sex	Age (years)	Rhythm	Δ t (months)	E F1 (mm / sec)	E F2 (mm / sec)	Δ E F (mm / sec)	D E1 (mm)	D E2 (mm)	MAIC 1 (mm)	MAIC 2 (mm)	DE/MAIC 1	DE/MAIC 2	Δ DE/MAIC
A M	F	40	NSR	13	41	41	0	16	15	10	10	1 6	1.5	−0 1
C F	F	39	NSR	10	54	52	− 2	18	18	–	–	–	–	–
F E	F	41	NSR	88	3[illegible]	32	− 3	15	13	10	9	1 5	1 4	−0 1
G R	F	4[illegible]	NSR	8[illegible]	50	43	− 7	22	20	16	14	1 4	1 4	0
G D	F	50	NSR	59	51	40	−11	1[illegible]	12	10	8	1 7	1.5	−0.2
H A	F	49	NSR	50	37	28	− 9	16	16	–	–	–	–	–
H \	F	3[illegible]	NSR	37	62	43	−19	20	18	10	10	2 0	1.8	−0.2
K I	F	4[illegible]	NSR	8	53	46	− 7	18	17	–	–	–	–	–
N R	M	38	NSR	60	75	55	−20	19	18	12	11	1 6	1 6	0
R I	F	41	NSR	3[illegible]	59	46	− 4	19	14	11	10	1 7	1 4	−0.3
R C	F	4[illegible]	NSR	6	25	24	− 1	15	14	–	–	–	–	–
R W	F	39	NSR	60	54	54	0	20	16	12	10	1 [illegible]	1 6	−0 1
S M	F	4[illegible]	NSR	78	82	62	−20	1[illegible]	17	10	10	1 7	1 7	0
Y K	F	41	NSR	74	76	58	−18	22	20	12	12	1.8	1 7	−0 1
W T	F	49	NSR	48	[illegible]6	32	− 4	18	18	–	–	–	–	–
D W	F	41	AF	9[illegible]	44	40	− 4	18	18	10	10	1.8	1.8	0
D A	F	4	AF	34	[illegible]8	[illegible]0	− 8	15	13	10	10	1 5	1.3	−0.2
R A	F	–	AF	3	60	57	− 3	20	20	–	–	–	–	–
S E	F		AF	44	[illegible]7	[illegible]	−12	20	[illegible]0	–	–	–	–	–
S L	F	4[illegible]	AF	[illegible]	43	34	− 9	19	14	12	11	1 7	1.3	−0 4
L W	F	44	AF		[illegible]	48	− 4	19	18	–	–	–	–	–
Mean		4[illegible]		[illegible]	[illegible]	44.8	− 7.8[illegible]	18.2	16 6	11 2	10 4	1 7	1.5	−0.13
SEM		1 8		[illegible]	[illegible] 2	2 3	1 43	0.5	0 6	0.5	0 4	0 04	0 0[illegible]	0 0[illegible]
p <					0 0005			0 0005		0 005		0 0025		0.[illegible]
2 SD							13 1[illegible]							

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Table III Correlation between the change of echocardiographic parameters and interval between two measurements (Δ t) in patients with mitral stenosis

	Δ EF	Δ DE	Δ MAIC	Δ DE/MAIC
r	−0 55	−0 48	−0.30	−0 42
p	>0 05	>0 05		
	<0 1	<0 1	>0 1	>0 1

Table IV Correlation between the change of echocardiographic parameters and interval between two measurements (Δ t) in patients following open commissurotomy

	Δ EF	Δ DE	Δ MAIC	Δ DE/MAIC
r	−0 29	−0 23	−0 33	−0 40
p	>0 1	>0 1	>0 1	>0 1

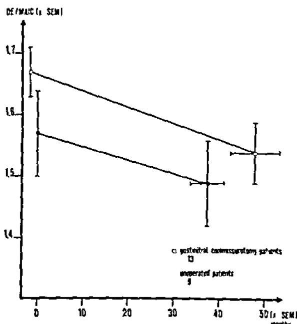


Fig 3 DE/MAIC index in mitral stenosis *(closed circles)* and after open commissurotomy *(open squares)* Δ t represents time elapsed between the two recordings

cardiogram due to intervening surgery However it is clear that our group represents a selected sample of the various stages of this disease since surgery cannot be withheld from the more severe cases We observed a slight though clinically inapparent progression of mitral stenosis which did however not correlate significantly with the interval between the two examinations (r = −0 55 p < 0 1 Table III) Three of 13 patients (23%) showed a significant progression defined as a slowing of the E F slope and/or a diminution of the DE/MAIC index of more than 2 SD (Δ E F and Δ DE/MAIC respectively) Dubin and colleagues in a hemodynamic follow up study of a similar group of patients with mitral stenosis found progression in 18 of 42 (43%) non operated patients over 3 7 years They indicate that this ratio is probably too high a statement which is corroborated by our findings In a study of the natural history of mitral stenosis Selzer and Cohn found that the disease may show very slow progression in some patients and may worsen rapidly in others depending on the degree of involvement of the mitral apparatus by the rheumatic process As shown in our study and by Dubin and colleagues mild mitral stenosis is associated with only minimal progression over 3 years This progression is just detectable by echocardiography

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In conclusion we feel that follow up examinations of patients with mild mitral stenosis and asymptomatic patients after mitral commissurotomy need to be repeated only every 3 years approximately

Summary

Thirteen patients with mild mitral stenosis and 21 asymptomatic patients after commissurotomy were studied by echocardiography in order to assess the rate of progression of mitral stenosis and the incidence of restenosis after successful open mitral commissurotomy In the group with

mitral stenosis there was a decrease of the diastolic closing velocity (E F slope) from 35 7 to 29 5 mm /sec ($p < 0.0005$) over a period of 37 months In 23% of the patients the stenosis increased significantly ($p < 0.0005$) by echocardiographic parameters

Forty eight months after commissurotomy we noted a significant over all slowing of the diastolic closing velocity (from 52 6 to 44 8 mm /sec $p < 0.0005$) and a decrease of the mitral valve closure index DE/MAIC (from 1 7 to 1 5 $p < 0.0025$) Five of 21 patients (24%) showed a change in one or both of these parameters which was greater than 2 standard deviations of the mean change Based on echocardiographic criteria we conclude that patients with mild mitral stenosis and asymptomatic patients following successful commissurotomy need only be checked approximately every 3 years

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Isolated ultrafiltration in the therapy of volume overload accompanying oliguric vascular shock states

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The continued presence of hypotension pulmonary edema and diuretic resistant oliguria in vascular shock states carries a grave prognosis even with agressive medical management Pulmonary edema in these patients has been shown to be related to decreased colloid osmotic pressure and/or increased pulmonary capillary wedge pressure [1,3]

Recent reports have not only shown that isolated ultrafiltration may be hemodynamically well tolerated in unstable patients [4] but that patients with congestive heart failure and edema without hypotension might effectively be treated with isolated ultrafiltration (without dialysis)

Coupling these reports we decided to attempt to reduce pulmonary edema via isolated ultrafiltration in three essentially pre terminal patients refractory to medical therapy Marked clinical improvement was noted in two of three patients and hemodynamic improvement was noted in all three patients We suggest that this mode of therapy may act by both decreasing pulmonary capillary wedge pressure and by increasing colloid osmotic pressure

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Methods

All patients were hospitalized in the intensive care units of the Medical College of Georgia Hospital (MCGH) All patients were continuously monitored by Swan Ganz catheters (triple or quadruple lumen) arterial pressure monitoring catheters and in some instances central venous pressure (CVP) monitoring catheters In all instances the catheters were connected to a Hewlett Packard 78304A oscilloscope after calibration was carried out both electronically and also using a mercury manometer The reference level for zero pressure was halfway between the sternum and the surface of the bed at the level of the fourth interspace The distal tip of the Swan Ganz catheter was in each instance positioned in the pulmonary artery according to previously described technique and its position was confirmed by portable chest roentgenogram Pulmonary capillary wedge pressure was recorded by intermittent inflation of the catheter balloon

Cardiac output determinations when measured were made using the thermodilution technique and by employing the Edwards Laboratories Model 9520 themodilution cardiac output computer All the monitoring lines had been placed to aid in the medical management of the patients prior to any consideration for ultrafiltration thus the introduction of femoral catheters was the only additional invasive procedure required

The unproved nature of ultrafiltration in the treatment of volume overload associated with vascular shock states was fully explained to the

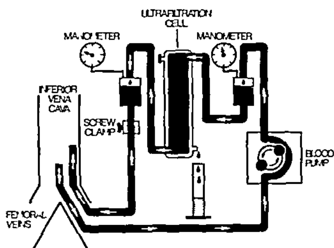


Fig 1 Arrangement of components for isolated ultrafiltration without dialysis (From Gerhardt R E et al Isolated ultrafiltration in the treatment of fluid overload in cardiogenic shock, Arch Intern Med. 139 358 1979 Reproduced with permission)

patient and/or next of kin and informed consent for the procedure was obtained in each instance

Percutaneous unilateral femoral vein catheterization with two catheters was performed using Shaldon s technique the venous return catheter was positioned approximately 6 cm proximal to the arterial outflow to minimize recirculation The extracorporeal circuit was arranged as shown (Fig 1) with monitoring of the extracorporeal pressure proximal and distal to the ultrafiltration cell A Gambro Ultradiffuser artificial kidney was used as the ultrafiltration cell and positive transmembrane pressure was applied via a screw clamp on the venous return to permit a transmembrane pressure of 300 to 400 mm Hg at a blood flow rate of 200 ml /minute This particular artificial kidney incorporates a high flux 11 5μ thick Cuprophane membrane with an active surface area of 1 86 M permitting removal of approximately 50 ml /minute of plasma water at a transmembrane pressure of 350 mm Hg

The ultrafiltrate was collected in a graduated cylinder for ease of measurement Low dose heparin therapy was given during the ultrafiltration and the heparin effects were reversed with protamine sulfate at the termination of the procedure

Case histories

Patient No 1 A 44 year old man suffered second and third-degree burns of 70% of his body surface During the first 4 days of hospitalization

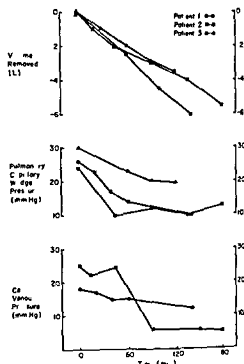


Fig 2 Plasma water removed and hemodynamic changes with isolated ultrafiltration in three patients with resistant fluid overload

the patient was treated with débridement fluid therapy and standard burn therapy Urine output remained good despite a decrease in pulmonary wedge pressure and central venous pressure (CVP) On the fourth and fifth days wedge pressure and CVP increased with an increase in administered colloid and fluid.

On the sixth day blood pressure fell rapidly tachycardia developed anuria occurred and it was felt the patient was suffering from septic shock. Over the next several hours approximately 17 liters of fluid and pressors were needed to maintain any blood pressure Despite intravenous glucocorticoids pressors (dopamine and norepinephrine) antibiotics and large doses of diuretics pulmonary edema hypotension and anuria persisted

When initially seen by us pulmonary capillary wedge pressure was 30 mm Hg peripheral arterial pressure was 100/60 with pressors and urine output was zero despite 500 mg intravenous furosemide Serum total CO was 20 0 mEq /L with a pH of 7 38 and a BUN of 32 Because of marked pulmonary edema manifested by physical examination chest roentgenogram wedge pressure and prompted by a declining arterial PO despite an FIO of 1 0 and the failure to improve

or diurese with conventional therapy isolated ultrafiltration was performed Blood pressure was stable throughout the procedure but despite temporary hemodynamic improvement with ultrafiltration (Fig 2) the patient died later that day

Patient No 2 A 54 year old man with known arteriosclerotic coronary vascular disease hypertension renal insufficiency (serum creatinine 4 0 mg /dl) and previous myocardial infarctions was transferred to MCGH after a cardiopulmonary arrest at another hospital He had become oliguric and volume overloaded at the other hospital and an attempt to perform peritoneal dialysis had resulted in bowel perforation The patient had had multiple transudative pleural effusions in the past

On transfer the patient was comatose anuric intubated and required assisted ventilation with blood pressure of 160/100 maintained with pressors Peripheral edema (4+) was present and a large right pleural effusion and pulmonary edema were also present Serum sodium was 131 mEq L, chloride 105 mEq /L potassium 5 6 mEq /L and total CO content was 17 mM/L While the patient was receiving an FIO of 0 4 arterial pO was 147 mm Hg pH was 7 32 and pCO was 32 mm Hg Despite continued pressors nitroprusside and intravenous furosemide anuria persisted central venous pressure was 35 mm Hg and wedge pressure was 24 mm Hg A chest tube was placed for drainage of the pleural fluid but failed to expand the right lung Because of continued deterioration and failure to respond to medical therapy ultrafiltration was performed with improvement of hemodynamic parameters (Fig 2) and clinical improvement but without any increase in urine output Blood pressure decreased transiently near the end of the procedure probably from excessive volume loss but returned to baseline after reinfusion of the blood in the extracorporeal circuit Studies obtained at the termination of the ultrafiltration procedure revealed an arterial pH of 7 31 a pCO of 26 mm Hg a total CO content of 15 mM/L with sodium of 135 mEq /L potassium 4 8 mEq /L and chloride of 105 mEq /L

Sepsis possibly from peritonitis occurred and the patient died five days after admission probably from another myocardial infarction Autopsy was not permitted

Patient No 3 A 55 year old woman with a



Fig 3 A and B *A* Anteroposterior chest roentgenogram of patient No 3 made immediately before ultrafiltration showing severe pulmonary edema *B* Anteroposterior chest roentgenogram of patient No 3 taken immediately after ultrafiltration showing marked decrease in pulmonary edema

history of diabetes mellitus arteriosclerotic coronary vascular disease previous myocardial infarction and mild renal insufficiency (serum creatinine 2 5 mg /dl) was transferred to MCGH after suffering another myocardial infarction accompanied by refractory congestive heart failure

On arrival the patient was in severe respiratory failure with rales over the lower three fourths of both lung fields blood pressure was 90/70 The neck veins were distended +2 peripheral edema was present and pulmonary capillary wedge pressure was 30 mm Hg cardiac output was 3 0 L/minute Despite vigorous therapy with dopamine nitroprusside atropine (for bradycardia) and large doses of intravenous furosemide anuria persisted and her continued deterioration required endotracheal intubation and assisted

ventilation Prior to ultrafiltration while intubated and receiving an FIO of 1 0 pO was 57 mm Hg pCO was 51 mm Hg with a pH of 7 31 and total CO content was 26 mM/L

Ultrafiltration was performed with marked improvement in hemodynamic (Fig 2) clinical and roentgenographic (Fig 3) parameters Cardiac output increased at the end of ultrafiltration to 4 9 L/minute At the termination of ultrafiltration while receiving an FIO of 0 5 but without other changes in the respiratory therapy pO was 144 mm Hg pH was 7 45 with a pCO of 31 mm Hg and a total CO content of 22 mM/L Urine output returned and increased to 100 ml/hr systemic pressure transiently decreased near the end of ultrafiltration but increased to 110/80 with the return of the blood in the extracorporeal circuit and nitroprusside and dopamine were gradually discontinued The patient was discharged four weeks after admission serum creatinine on discharge was 3 0 mg/dl

Results

Clinical improvement was noted in two patients (Nos 2 and 3) with improved oxygenation and decreased physical findings of congestive heart failure The chest roentgenograms supported the clinical findings of lessened failure (Fig 3)

Marked improvement was noted in the measured parameters in all three patients (Fig 2) Pulmonary capillary wedge pressure declined as did central venous pressure during the ultrafiltration therapy Cardiac output measured in patient No 3 also improved Despite the grave clinical situations presented by these patients including marked hypotension (resistant to pressors in cases Nos 1 and 3) the procedure was well tolerated by the patients the hemodynamic status improved in each case and one patient survived to be discharged from the hospital In two of the three cases (Nos 2 and 3) transient increases in hypotension occurred near the end of ultrafiltration probably heralding the onset of intravascular volume depletion and maximum extravascular to intravascular volume shifts In both cases blood pressure increased to baseline or above with the termination of ultrafiltration and the return of the blood in the extracorporeal circuit

Concurrent analysis of the ultrafiltrate revealed that as reported it had the composition of plasma water with essentially no protein content No hemolysis reported to possibly occur with the use of positive pressure ultrafiltration[1] was noted

Discussion

In patients with shock states particularly after myocardial infarction it is important to obtain hemodynamic data to assess the presence of pulmonary congestion and the appropriate therapy[11] In the group of patients with volume overload pulmonary edema hypoxia and elevated pulmonary wedge pressures one of the mainstays of therapy is reduction of volume by use of potent diuretics[1] If these patients are refractory to medical therapy including pressors diuretics, and preload and/or afterload reduction prognosis is grave Rotating tourniquets will decrease preload but are only a temporary therapy unless adequate diuresis can be established Peritoneal dialysis is too slow and may further compromise respiratory movements Thus a reasonably easy means of removing fluid while maintaining or increasing colloid osmotic pressure has not been generally available in the past

Although ultrafiltration during hemodialysis is a routine clinical practice the occurrence of hypotension and tachycardia—possibly related to simultaneous changes in blood volume and osmolality—limits the amount of fluid that can be removed asymptomatically Bergstrom and colleagues have recently demonstrated that isolated ultrafiltration (without dialysis) is remarkably well tolerated in fluid overloaded patients without the development of the hemodynamic instability associated with combined ultrafiltration and dialysis

In dialysis patients isolated ultrafiltration can be performed via conventional vascular access In emergency situations in hypotensive patients peripheral access sites will not provide enough blood flow for adequate ultrafiltration However femoral vein access via Shaldon s technique provides a rapid safe access to a large vascular reservoir Ultrafiltration from this pool has the advantages of being relatively independent of peripheral blood pressure and at the same time directly decreases venous pressure and venous return to the heart while possibly augmenting the colloid osmotic pressure in the pulmonary vasculature

The application of isolated ultrafiltration in

the treatment of generalized edema often related to cardiac disease has been reported[6,7] however it does not appear that these patients were systemically hypotensive only two of the patients reported by Asaba and associates[7] appeared to be hypotensive and it does not appear that they were in shock A single case report details the use of isolated ultrafiltration in the therapy of volume overload accompanying cardiogenic shock[12]

We have applied the technique of isolated ultrafiltration to critically ill essentially preterminal hypotensive patients with life threatening fluid overload refractory to other forms of medical management The patients tolerated the procedure well in all instances with marked improvement in hemodynamic parameters (Fig 2) and rapid improvement of the chest roentgenogram

Our analysis of the ultrafiltrate which is in agreement with other reports suggests that the clinical improvement may be related to both decreased volume and increased plasma oncotic pressure Since large volumes of water are removed by the ultrafiltration cell without loss of protein the oncotic pressure of the blood returning to the patient from the cell must be increased The effect of this increase may be augmented removal of interstitial fluid from the pulmonary parenchyma Indeed increases of serum albumin (the major component of plasma oncotic pressure) have been shown to occur with isolated ultrafiltration[7]

Although further evaluation of the mechanism of the improvement remains to be elucidated we feel that the process of isolated ultrafiltration may have clinical application in the treatment of severe fluid overload even in that group of severely ill patients with significant hypotension

Summary

Isolated ultrafiltration (removal of plasma water and solute without dialysis) was used as a last resort therapy in three patients with diuretic and pressor resistant oliguria complicating severe volume overload and vascular shock The improvement in clinical and hemodynamic parameters is reported and the possible mechanisms of action (decreased pulmonary capillary wedge pressure and increased colloid osmotic pressure) are discussed

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Exercise testing: A prospective study of complication rates

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Exercise testing has become a well established clinical method for determining the work capacity of patients and has gained widespread acceptance in cardiology as a non invasive tool for the diagnosis and functional evaluation of heart diseases. The various types of exercise stress tests described[5, 7, 13, 1, 9] which include step tests, bicycle ergometry tests, and treadmill tests all involve certain risk factors. It has been emphasized that a standardized procedure is a prerequisite for the satisfactory accomplishment of these tests in the clinical evaluation of patients.[11, 1, 16] Generally accepted rules for what types of patients should be excluded from exercise stress testing and for interruption of the test in order not to expose the patients to unnecessary risks are, however, still lacking. Retrospective studies of mortality rates in association with exercise stress testing have been carried out previously but no prospective study covering the rate of exercise induced mortality or non fatal complications appears to have been reported.

In order to examine both how exercise stress testing is performed in Swedish hospitals today and the rates of exercise induced complications a multicenter study has been undertaken based on questionnaires and an 18 month prospective follow up of complications. The results are presented in this report.

Methods

Exercise stress testing of patients in Sweden is mainly carried out in the hospital departments of clinical physiology. Questionnaires concerning the mode of performance of exercise testing were sent to all these departments in Sweden. Twenty out of the 24 departments replied. These 20 departments then took part in an 18 month study of complications related to exercise testing. During the period of the study about 50,000 exercise tests were accomplished. A complication was defined as a reaction occurring during or within 24 hours after the test constituting a risk of or leading to morbidity or mortality. Sinus bradycardia was defined as a sinus rhythm of less than 40 beats/minute, ventricular tachycardia as 10 or more consecutive ventricular extrasystoles (VES), and a fall in systolic blood pressure as a reduction of 25 mm Hg or more during the exercise. Appearance of A V block grade I, right bundle branch block, and pre exitation was not defined as a complication.

Statistical methods. We denote by N the number of tests performed and by X_i the number of a certain complication arising during the tests. Since a complication occurring during exercise testing must be considered as rare, the incidence rates can be estimated as follows. We assume that the X's are normally distributed with expectation $f_i N$ and variance $f_i N$. The f_i is estimated by the incidence rates $\hat{f}_i = X_i/N$ and 95% confidence limits are obtained as $\hat{f}_i \pm 1.96\sqrt{(\hat{f}_i/N)}$.

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Table I Starting and increments of load and duration of steps used routinely in exercise testing with bicycle ergometry

	Starting load		*Load increment*		*Step duration*	
	W	*n*	W	*n*	*min*	*n*
Men	20	1	10	1	1	1
	50	19	50	19	4	3
					4/6	3
					6	13
Women	10	1	10	1	1	1
	30	15	30	14	4	4
	33-40	4	30/40	4	4/6	2
			33	1	6	13

W = watts n = number of hospitals.

Table II Duration of load steps used in bicycle ergometry in different diseases

	Continuous increment *n*	*1 min* *n*	*4 min* *n*	*6 min* *n*
Health control	0	1	7	12
After acute myocardial infarction	1	5	6	8
Angina pectoris	1	7	6	6
Obstructive pulmonary disease	0	3	6	11

n = number of hospitals

Results

Type of exercise test and load increment In all hospitals the physician responsible for the exercise test routinely takes the case history of patients with cardiac or pulmonary disease prior to the test In 80% of the hospitals all patients undergo physical examination routinely immediately before the exercise test In the case of most diseases *e g* valvular heart disease coronary insufficiency cardiac arrhythmias obstructive and restrictive pulmonary disease and also in health examinations the exercise tests are performed almost exclusively on an electrically braked bicycle ergometer A treadmill is used routinely in 25% of the hospitals in exercise testing of patients with intermittent claudication and in 10% after a recent myocardial infarction In patients incapable of using their legs the test is performed with a bicycle ergometer adapted for arm work Step tests are not used

The exercise test is performed with a continuous load increase or stepwide load increments where the duration of each load is 1 4 or 6 minutes dependent on the patient s condition (Table I) The tests are generally symptom limited but in all hospitals the routine tests is discontinued at a submaximal work load regarding oxygen uptake capacity As seen in Table II small load increases with short load intervals are used mainly in patients with coronary insufficiency (angina pectoris recent myocardial infarction) In all hospitals ECG blood pressure and respiratory frequency are routinely recorded during the test In patients with pulmonary disease peak expiratory flow (PEF) is usually also checked Blood sampling for analysis of blood gases acid base status lactate and blood sugar is only done in special examinations

Criteria for exclusion of patients from exercise testing and discontinuation of the test The policy regarding exclusion of patients from exercise testing is presented in Table III In 25% of the hospitals no general limits or criteria are used for the discontinuation of an exercise test (Table IV) and this is based on individual evaluation with regard to the patient s diagnosis and age In all hospitals the exercise test is discontinued on occurrence of chest pain of the angina pectoris type but in some hospitals the pain must be severe or increasing in intensity to fulfill this criterion Appearance of frequent multiform or coupled VES supraventricular tachycardia pre excitation or bundle branch block during exercise is accepted as a criterion for discontinuation

Some diseases give reason for special caution during the course of an exercise test In valvular heart disease especially aortic stenosis particular observance is paid to symptoms such as dizziness dyspnea fall in blood pressure or absence of a blood pressure increase In many hospitals when exercise testing patients with recent myocardial infarction the test is discontinued at a lower heart rate than normally and in patients with cardiac decompensation special attention is paid to signs of left ventricular failure In patients with obstructive or restrictive pulmonary disease

Table III Criteria for exclusion from exercise testing

	Absolute exclusion performed *n*	*Time limit alt limit value*		*Absolute exclusion not performed* *n*
			n	
Valvular heart disease	0			20
Fever disease	18	–		2
After acute myocardial infarction	16	2 4 weeks	12	
		4 8 weeks	3	4
		12 weeks	1	
After acute myocarditis	13	2 4 weeks	11	
		8 12 weeks	2	7
Heart decompensation at rest	12			8
Unstable angina pectoris	6	1 2 weeks	2	
		2 4 weeks	4	14
Hypertension	6	Syst BP 210 230	3	
		[mm Hg] 250 270	3	14
After heart arrhythmia	4	1 week	4	16
Increased heart rate at rest	3	HR 120 150 beats/min	3	17
After syncope	2	–		18
Electrolyte disturbance	2	–		18

n = number of hospitals

attention is paid to the occurrence of extra sounds on pulmonary auscultation and to signs of right ventricular insufficiency

No type of medication implies exclusion from an exercise test in any of the hospitals In 40% of the hospitals however it is routine practice to interrupt digitalis medication 2 to 6 weeks (median 3 weeks) before the test and in 30% for beta receptor blockers to be stopped 1 to 4 days (median 4 days) before the test The presence of a physician during the exercise test depends upon the condition of the patient Forty % of the hospitals report that a physician is present throughout the exercise test in health examinations For patients after recent myocardial infarction this is reported by 85% In all hospitals the ECG is monitored continuously throughout all tests All hospitals have immediate access to a defibrillator and other equipment for emergency cardiopulmonary resuscitation and support

Complications Ninety two complications (29 women and 63 men) were reported by the 20 hospitals during the 18 months of the study In 82% of these cases the patients were 50 years of age or more None of the patients with complications was below 20 years As seen in Table V supraventricular and ventricular tachyarrhythmias fall in systolic blood pressure and acute myocardial infarction constituted the most frequently reported complications Ventricular fibrillation as a sole complication was reported in one patient with coronary insufficiency In three patients with known coronary insufficiency acute myocardial infarction associated with ventricular fibrillation was elicited Recovery was immediate in 67 of the 92 complications In 26 patients the complication led to hospitalization altered medication or follow up examinations and was classified as morbidity Two of these patients died One with severe aortic stenosis had a blood pressure fall during the exercise with bradycardia and asystole that later turned into ventricular fibrillation and after defibrillation into therapy resistant bradycardia with pulselessness The other patient died two hours after the test in acute myocardial infarction with ventricular fibrillation when resuscitative attempts failed Of the two patients with a cerebrovascular lesion (CVL) one with persistent regular heart rhythm had syncope during the test Consciousness was regained within 10 seconds after interruption of exercise and there were no persistent neurological symptoms The other patient developed hemiparesis during the test which disappeared totally within a few hours Twenty one of the 92 complications started after discontinuation of the exercise 17 of these within 10 minutes and four (all acute myocardial infarction) between 2 and 18 hours after the test

Table VI shows the work load heart rate systolic blood pressure and respiratory frequency recorded immediately prior to the four most

Table IV Criteria for completion of exercise testing

	Limit value used	*n*	*Not used n*	*Not answered n*
Syst blood pressure during exercise (SBP mm Hg)	SBP = 240	1		
	= 250 5	7	6	0
	= 280 300	6		
Heart rate (HR beats/min)	HR = 150 1 0	1		
	= 1 0	3	9	0
	= 200 240	2		
	Age related max value	5		
Syst blood pressure fall during exercise (SBPF mm Hg)	SBPF = 5 10	4	6	5
	= 15 0	5		
Breathing frequency (f breaths/min)	f = 30	1		
	f = 31-40	5	7	5
	f = 41 50	2		
ECG-changes				
S-T elevation (STE mm)	STE = 1 2	4		
	= 3 5	2	7	6
	= 8	1		
S-T depression (STD mm)	STD = 1 [illegible]	3		
	= 3 [illegible]	5	6	4
	= 8 10	2		
T wave changes		4	6	10

n = number of hospitals

frequent complications The majority of complications were initiated at a heart rate of 150 beats/minute or below a systolic blood pressure of 200 mm Hg or below and a respiratory frequency of 30 breaths/minute or below

In Table VII the complications are distributed according to the patients main disorders In 89[illegible] of the cases with complications the main disorder was a heart disease The most frequently occurring diagnoses were suspected or proved ischemic heart disease (IHD) valvular heart disease and heart arrhythmias Among the valvular heart diseases aortic stenosis showed a higher frequency than the others combined In suspected or proved IHD practically all types of complications were recorded whereas blood pressure fall was the dominant complication in aortic stenosis In patients with heart arrhythmias as the main disorder arrhythmias also constituted the dominating complication

In Table VIII the work load heart rate systolic blood pressure and breathing frequency recorded during the test immediately prior to the complication are cross tabulated with three of the main types of disorders namely IHD heart arrhythmias and aortic stenosis In the latter a fall in systolic blood pressure constituted the

Table V Number of complications in association with exercise testing (50 000 tests)

Complication	*Number*	*Morbidity*	*Fatal outcome*
Bradyarrhythmias			
Sinus bradycardia (≤ 40 beats/min)	4		
Asystole	2	1	1
Supraventricular tachyarrhythmias			
Atrial tachycardia	10	1	
Nodal tachycardia	2		
Atrial fibrillation	4	4	
Atrial flutter	1	1	
Ventricular tachyarrhythmias			
Ventricular tachycardia (≥ 10 consecutive VES)	29	6	
Ventricular fibrillation	1	1	
Conduction disturbances			
Second-degree AV block	1	1	
Left bundle branch block	1	1	
Systolic blood pressure fall (≥ 25 mm Hg)	26	1	
Acute myocardial infarction	7	7	1
Pulmonary edema	2		
Cerebrovascular lesion	2	2	
Total	92	26	2
Incidence per 10 000 tests	18 40	5.20	0 40
95 per cent confidence	14 6 22.2	3.2 7.2	0 0- 0.95

Table VI Distribution of complications (n = per cent of total number of that complication) at different levels of work load heart rate systolic blood pressure and breathing frequency

Complication	Work load (watt)				Heart rate (beats/min)				
	-50	51 100	101 150	151 200	100	101 125	126 150	151 175	176
Supraventricular tachyarrhythmia	12	35	47	6	6	12	41	35	6
Ventricular tachyarrhythmia	16	47	27	10	10	20	36	27	[illegible]
Systolic blood pressure fall	16	68	8	8	28	24	40	8	
Acute myocardial infarction	57	29	14		29	29	13	29	

Complication	Syst blood pressure (mm. Hg)				Breathing frequency (breaths/min)			
	150	151 200	201 250	250	20	21 30	31-40	41-50
Supraventricular tachyarrhythmia	6	65	29		50	38	12	
Ventricular tachyarrhythmia	21	39	35	4	36	52	12	
Systolic blood pressure fall	28	48	20	4	32	5	12	4
Acute myocardial infarction	29	57	14		33	67		

Table VII Number and sort of complications that occurred in the different main disorders

Main disorder	CVL	Sinus bradycardia	Asystole	Supraventricular tachyarrhythmia	Ventricular tachyarrhythmia	Conduct disturb	Syst Bl fall	Acute myocard infarct	Pulm. edema
Suspected or proved IHD	1	1		4	15	1	3	-	
Valvular heart disease									
Aortic stenosis			1		3		8		
Aortic insufficiency				1	1				
Mitral stenosis				2			3		
Mitral insufficiency				1	2				
Heart arrhythmias				4	5	1	9		
Heart decompensation		1		2	1				
Intermittent claudication	1	1		1					
Hypertension		1					1		
Uremia diabetes chronic bronchitis etc			1	2	3		2		
Total		4	2	17	30	2	26	7	

CVL = cerebrovascular lesion

main complication In the five most severe cases of aortic stenosis complications occurred at a work load of 60 W or below and at a systolic blood pressure at 140 mm Hg or below There seemed to be no connection between the magnitude of these variables and the incidence of complication in patients with IHD or heart arrhythmias Likewise no connection was found between the types and rates of complications reported and the criteria used for exclusion from and discontinuation of exercise tests shown in Tables III and IV

Discussion

Exercise stress tests are widely used in diagnostic and prognostic evaluations and assessment of work capacity in different disorders especially in cardiac diseases[1-3] However the procedures still involve a risk of precipitating morbidity and even mortality which is related to the type and severity of the disease Therefore further objective evaluation of the techniques before general use in the clinical routine has been proposed. However others maintain that if adequate safety measures are employed the benefits of exercise

Table VIII Distribution of complications that occurred in the three main disorders (n = per cent of total number of complications in that disorder) at different levels of work load heart rate systolic blood pressure and breathing frequency

	Work load (watt)				Heart rate (beats/min)				
	≤50	51 100	101 150	151 200	100	101 125	126 150	151 175	≥176
Susp or proved IHD	20	52	18	10	25	25	30	15	5
Heart arrhythmias	8	38	46	8	15	0	54	31	
Aortic stenosis	25	67	0	8	8	17	50	25	

	Syst blood pressure (mm Hg)				Breathing frequency (breaths/min)			
	≤150	151 200	201 250	>250	≤20	21-30	31-40	41-50
Susp or proved IHD	24	46	27	3	41	53	3	3
Heart arrhythmias	16	46	38		4	50	8	
Aortic stenosis	67	8	25		10	60	20	10

tests make the cost yield balance of the tests favorable in comparison to a number of other clinical procedures[6, 9] The various types of exercise tests that have been described are mainly variations of step tests bicycle ergometry and treadmill tests [10] Today information is lacking regarding presumptive differences in complication rates between these methods It is clear that as the use extends there is a need to assess the techniques and to outline the optimal application of these tests

Bicycle ergometry has now been used in clinical practice in Sweden for 30 years [1] and as is shown in this study this technique is predominant among the different exercise tests used in Sweden [1] Reasons for the popularity of bicycle ergometry are that it is simple to use and work intensity can be measured without determination of the oxygen uptake The relative immobility of the upper part of the body during testing with this technique makes it easy to obtain good electrocardiographic recordings and to measure the blood pressure and other variables for the prevention of accidents Thereby the patient can be continuously carefully supervised during the procedure In the vast majority of hospitals the standards of practice employed are high and adequate safety precautions are observed

Although the standard procedures of the tests are similar this investigation shows that the criteria for exclusion from and interruption of exercise stress tests differ from one hospital to another Since patients with various heart diseases predominate in the clinical material the criteria for using the exercise test in this group of patients are of paramount interest There is little or no difference between the hospitals in the opinion that patients with valvular heart disease should not be excluded from exercise testing Likewise the majority of hospitals consider that patients who recently have had an acute myocardial infarction or acute myocarditis can be exposed to exercise stress testing but that the time limits for when this can be done vary In the majority of the hospitals patients with cardiac decompensation at rest unstable angina pectoris hypertension and cardiac arrhythmias are not generally excluded

This study has revealed a complication rate of 18 4 a morbidity rate of 5.2 and a mortality rate of 0 4 per 10 000 tests The morbidity rate was significantly higher than that found retrospectively by Rochmis and Blackburn of 2 4 per 10 000 tests The difference may be due to the prospective technique in our study probably resulting in higher reported rates of minor complications leading to morbidity Another explanation may be the nonrestrictive policy found in this study regarding criteria for exclusion from and interruption of work tests in patients with severe heart disease However the reported rates of severe morbidity eg myocardial infarction cerebrovascular lesions and persistent heart arrhythmias were low Our reported mortality

rate 0.4 per 10 000 tests is lower that that reported by Rochmis and Blackburn[17] of 1 per 10 000 tests. The latter figure is partly explained by a longer observation period (4 days) but it may also be due to differences in the types of tests and procedures between medical centers in the United States and Swedish hospitals.

It must be emphasized that when an occurrence of a phenomenon is very low, chance may give great variations in incidence from one sampling to another. In our study acute myocardial infarction occurred seven times as a complication to the exercise tests. A 95% confidence interval of this figure covers 1.8 to 12.9 cases, i.e. with 95% confidence the true value is somewhere between 1 and 13 cases.

The incidence of acute myocardial infarction in a representative Swedish population aged 40 to 70 years of both sexes is about 3.75 per 1 000 person years. The expected number of acute myocardial infarctions to occur during the 24 hours of observation after 50 000 exercise tests is 0.52 cases. However, our number of seven cases all occurred among patients with known IHD, a disease that has a higher incidence of myocardial infarction than the population in general. Accordingly, it is not possible to give an exact figure for an eventually increased rate of myocardial infarction due to exercise testing.

Two persons died in direct connection with an exercise test. The 95% confidence interval covers 0.00 to 4.75 cases with fatal outcome, i.e. 0.00 to 0.95 deaths per 10 000 tests with an observation time of 24 hours/test to be compared with the expected number of deaths, that is 0.24 deaths calculated from the 8.5 deaths per 1 000 person years due to all causes that occur in Sweden for persons aged 40 to 70 years.

The findings that 89% of the patients with complications suffered from suspected or proved heart disease and that 82% were at least 50 years old indicate that elderly patients with heart disease constitute a heavy risk group for complications during exercise testing. These observations are in line with the results reported by McNiece, that the incidence of supraventricular and ventricular extrasystoles during exercise testing increased with age and for any age group increased with the evidence of cardiovascular disease. However, as the majority of patients at Swedish hospital departments are in the higher age group and many exercise tests are performed because of heart disease, the significance of ou[r] findings is difficult to evaluate.

In the majority of cases included in this repor[t] the complications occurred at a heart rate of 1[5] beats/minute or below, a systolic blood pressur[e] of 200 mm Hg or below, and at a respirator[y] frequency of 30 breaths/minute or below. Th[is] shows that the fixed interrupting criteria used b[y] most of the hospitals are insufficient to guar[d] completely against complications. Howeve[r] further narrowing of the criteria will most proba[-]bly result in loss of valuable information.

As shown in this study, patients with aorti[c] stenosis obviously perform an exercise test with [a] high risk of complications, and it should b[e] observed that in patients with severe aortic steno[-]sis complications may occur at a low work load. In conclusion, it must be emphasized that whe[n] planning for an exercise test each case has to b[e] carefully evaluated as to whether or not th[e] benefits outweigh the risks of the test, especiall[y] in elderly patients with heart disease. Whe[n] exercise testing takes place, it is an absolu[te] requisite that the case history be taken an[d] physical examination performed prior to the test, that the ECG be monitored continuously dur[ing] and even up to 10 minutes after the test, that a physician trained in resuscitation be present and that emergency resuscitative equipment includ[-]ing a defibrillator be available. Under these circumstances exercise testing can be regarded as a safe method to be used in the evaluation of even very ill patients.

Summary

Twenty departments of clinical physiology in Sweden, doing annually 30 000 exercise stress tests mainly of patients, completed a question[-]naire regarding how they carried out exercise testing. Bicycle ergometry was predominantly used. The criteria for inclusion of patients for exercise testing and for interruption of the test were generally wide, allowing the patient to work until symptoms limited the test. In a second part of the investigation, the departments continuous[-]ly reported all complications that occurred during an 18 month period which included 50 000 exer[-]cise tests. The complication rate was 18.4, the morbidity rate was 5.2, and the mortality rate was 0.4 per 10 000 tests. The number of complications leading to permanent damage was low, and it could not be proved that the exercise test had

induced a higher complication rate than otherwise would have occurred during the observation period Patients with aortic stenosis had a high risk for complications With adequate safety measures and a well trained staff exercise stress testing can be regarded as a safe method to be used in the evaluation of even very ill patients

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The role of the intra-aortic balloon in cardiac anesthesia and surgery

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Since Clauss and associates[1] described the concept of counterpulsation in 1961 it has been used to reduce afterload or arterial impedance Their arterial counterpulsator withdrew blood from the aorta during systole and returned it during diastole The mechanism of its action was to reduce aortic and left ventricular systolic pressures, left ventricular wall tension and thus reduce myocardial oxygen consumption At the same time the increased aortic blood volume during diastole increased coronary perfusion Many other techniques of counterpulsation have been developed since 1961 but the intra aortic balloon pump (IABP) has become by far the most popular Moulopoulus and colleagues first produced diastolic augmentation in 1962, using a balloon catheter placed in the aorta Their studies were later adapted by Kantrowitz and co workers who perfected the technique in 1968 for clinical use in patients with cardiogenic shock. In 1970 Mundth and associates introduced the use of the intra aortic balloon to stabilize patients with cardiogenic shock in preparation for surgery And, in 1973 Buckley and colleagues[3] reported on the use of the IABP in patients who were unable to be weaned from cardiopulmonary bypa Since 1973 other reports have confirmed t beneficial effects of the IABP in cardioge shock after cardiopulmonary bypass.[4]

Recently some authors have recommended t prophylactic use of the IABP during card surgery before the induction of anesthesia a cardiopulmonary bypass Garcia and co-worke proposed the use of the IABP in all patients wi left main coronary artery disease Cooper a associates suggested it for all patients with p infarction or unstable angina and Goldman a colleagues recommended it for all corona revascularization patients with poor left ventric lar function

The purposes of this study were (1) to dete mine our incidence of use of the intra aort balloon (2) to re-evaluate the indications for t IABP during cardiac surgery and (3) to assess t hemodynamic effects of the IABP dur surgery

Methods and materials

Between January 1976 and December 197 1 738 adult cardiac operations were performed a Emory University Hospital One thousand tw hundred and three of the operations were cor nary revascularization procedures Computerize hospital records were retrospectively analyzed t determine all patients in whom the IABP wa inserted The hospital records of the 63 patients i whom the IABP was inserted were evaluated a to the type of surgery indications for the IABP time of insertion of the IABP other therapeuti interventions, and results of the surgery For th purposes of this study we divided its two-yea

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Table I A 24 month experience with the IABP

	Group	Jan -June 1976	July Dec 1976	Jan -June 1977	July Dec 1977	Totals	% of usage
IABP prior to operating room	I	1	1	6	–	8	12.70%
IABP pre bypass	II	5	3	3	2	13	20 63%
IABP post bypass	III	13	13	9	7	42	66 67%
Total use IABP		19	17	18	9	63	
Total cardiac surgery		310	372	536	520	1738	
% of cases with IABP		6 13%	4 5 %	3 36%	1 73%	3 62	

span into four six month periods to determine any changes in indications for the IABP or frequency of its use

The patients were divided into three groups Group I required the IABP before arrival in the operating room Group II had the IABP inserted electively in the operating room before cardiopulmonary bypass and Group III required the IABP at the end of bypass[11] The indications for the IABP in Groups I and II were (a) acute myocardial infarctions complicated by a mechanical defect (ventricular septal defects acute mitral insufficiency or ventricular aneurysms) continued ischemic pain and infarct extension or refractory ventricular tachyarrhythmias (b) extremely poor left ventricular function (ejection fraction < 0 25 and left ventricular end diastolic pressure > 25 torr) or cardiogenic shock or (c) combined extensive coronary and valvular heart disease Indications for the IABP after cardiopulmonary bypass were (a) inability to discontinue bypass within 30 minutes (b) inadequate hemodynamics after therapy with *both* an inotrope and a vasodilator (c) poor hemodynamics after drug therapy including a cardiac index less than 2 0 L/min/M² left atrial pressure greater than 20 torr systolic blood pressure less than 80 torr peripheral resistance greater than 2 500 dynes/sec/cm and urine output less than 0 5 ml/Kg/hr (d) epinephrine dose greater than 15 μg/minute or (e) persistent ventricular arrhythmias

Premedication was with morphine and scopolamine and in some patients diazepam was added Upon arrival in the operating room all patients had a 20-gauge radial artery catheter inserted and most had a No 7 French thermodilution Swan Ganz catheter placed via the right internal jugular vein Measurements of cardiac output total peripheral resistance (TPR) left ventricular stroke work index (LVSWI) pulmonary capillary wedge pressure (PCWP) and central venous pressure (CVP) were made in the awake state in all patients in Groups I and II and in some patients in Group III The induction of anesthesia was primarily accomplished with morphine 0 5 to 1 0 mg/Kg supplemented with diazepam nitrous oxide and pancuronium bromide Anesthesia was maintained with additional morphine nitrous oxide and intravenous nitroglycerin to control blood pressure and filling pressures[1]

Cardiovascular measurements were made in 11 patients with the IABP Six patients had measurements made before cardiopulmonary bypass in order to compare their baseline hemodynamics with the IABP off to those recorded when the IABP was augmenting each heart beat (1 1 mode) Serial measurements of hemodynamics were made both before and after bypass in these patients In addition five patients who required the IABP to discontinue cardiopulmonary bypass had hemodynamic measurements performed with the IABP in the 1 1 mode compared to the 1 8 mode

Table II IABP prior to cardiopulmonary bypass—distribution of patients (Groups I II N = 21)

Indication	Number	Survived
Complicated acute myocardial infarction (mechanical problem)	13	10
Group I	6	
Group II	7	
Poor left ventricular function or shock	7	6
Group I	2	
Group II	5	
Combined coronary and valvular heart disease (IHSS)	1	1
Group II	1	

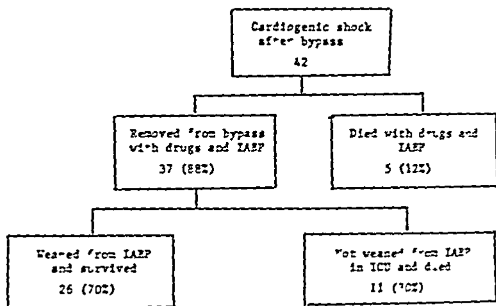


Fig 1 Results of patients requiring IABP after bypass

Results

In the 24 month period of the study 63 of 1 738 (3 62%) adult cardiac surgery patients received the IABP (Table I) At our institution there appeared to be a progressive decrease in the use of the IABP when taken as a percentage of the total cardiac operations. The incidence decreased from 6 13% of cases in early 1976 to 1 73% of cases in late 1977

One third of the IABPs were used in the period before cardiopulmonary bypass (Groups I and II) while two thirds were used after bypass. The distribution and results of the 21 patients who received the IABP before bypass are shown in Table II Most of the pre bypass use of the IABP in 1977 was for patients with complicated myocardial infarctions (nine of 11) while in 1976 many of the IABPs had been used for patients with poor left ventricular function (five of 10) There were four hospital deaths among these patients (19%) Three of the deaths were in patients with complicated acute infarctions

In 42 of the patients the IABP was placed after cardiopulmonary bypass All of the patients were in a profound low output state after maximum inotropic support with calcium chloride (1 to 2 grams) and either dopamine (5 to 25 µg/kg/min) or epinephrine [illegible] Most of the patients also received [illegible] or nitroprusside (20 to 100 µg/min [illegible] (32 128 µg/min) in an effort to decrease the left ventricular wall tension and their impedance to left ventricular ejection The surgical procedures performed in these 42 patients were coronary revascularization alone (15) coronary revascularization plus valve replacement (4) coronary revascularization plus ventricular aneurysm resection (5) single valve replacement (10) and multiple valve replacement or repeat valve replacement (8) Without the IABP many of the 42 patients would have died in the operating room Using the IABP combined with drug therapy only five patients died in the operating room while 11 others died postoperatively in the intensive care unit (Fig 1) Survival to discharge from the hospital was made possible by the IABP in [illegible] of the 42 patients (62%) who were in cardiogenic shock at the end of cardiopulmonary bypass Seventy per cent of the patients who were successfully weaned from bypass with the IABP survived the operative period In the entire study (Groups I II and III) 42 of the 63 patients (67%) who needed the IABP survived.

Hemodynamic measurements in six patients who had the IABP placed before bypass are shown in Table III The IABP decreased the systolic blood pressure (SBP) CVP PCWP and TPR while it increased the diastolic blood pressure (DBP) LVSWI and CI Five patients who required the IABP to discontinue cardiopulmonary bypass had intraoperative hemodynamic measurements made after they were tabulated

Table III Hemodynamics in 6 patients with the IABP before cardiopulmonary bypass

Patient	Surgery indications Cath data	BP (Torr)		CVP (Torr)		PCWP (Torr)		CI (L/min/M²)		LVSWI (Gm m/M²)		TPR (dynes/sec/cm⁻⁵)	
		C	1:1†	C	1:1	C	1:1	C	1:1	C	1:1	C	1:1
1	CABG (3) MVR CHF EF .41 LVEDP 14	90/68	75/90/55	6	5	2?	20	2.4	2.5	23	23	869	812
2	CABG (4) VA CHF EF .30 LVEDP 24	120/60	95/150/35	[illegible]	5	12	10	1.8	2.1	27	25	1985	1500
3	CABG (3) EF .25 LVEDP 35	128/75	115/120/68	11	11	14	12	2.1	2.3	25	30	1?90	1268
4	CABG (4) CHF EF .10 LVEDP 15	170/86	140/150/50		4	[illegible]	14	1.5	1.9	22	24	2100	1629
5	VA CHF EF .05 LVEDP 35	110/?0	110/150/30	10	6	22	16	1.?	1.8	14	19	1840	1683
6	CABG (3) EF .10 LVEDP 25	150/74	144/160/60	8	5	21	7	1.8	2.4	37	57	1899	1690
	EF LVEDP												
x̄	.20 25	128/72	113/13?/48	8	6	20	13	1.9	2.2	25	30	1?47	1430
SE	.005 3.8	11.7/3.5	10.8/10.9/5.3	.8	1.0	2.3	1.9	.1	.1	3.1	5.7	181	140

P < .05 by Student's t test.
C = control baseline hemodynamics 1:1 = IABP on 1:1 mode CABG = coronary artery bypass graft MVR = mitral valve replacement CHF = congestive heart failure VA = ventricular aneurysm.
† = systolic pressure/balloon augmented diastolic pressure/diastolic pressure

Table IV Hemodynamics in 5 patients who required the IABP after cardiopulmonary bypass

Patient	Surgery indications Cath data	BP (Torr)		PCWP (Torr)		CI (L/min/M²)		LVSWI (Gm m/M²)		TPR dynes/sec/cm⁻⁵		EVR		Drugs
		1:8	1:1	1:8	1:1	1:8	1:1	1:8	1:1	1:8	1:1	1:8	1:1	
1	CABG (4) VA EF .30 LVEDP 24	112/64	90/115/40	12	10	1.8	2.3	14	18	1889	1148	?9	2.0	Dopamine 3μg/Kg/min
2	CABG (3) EF .25 LVEDP 35	140/85	100/110/50	14	11	2.0	1.9	47	48	2022	1459	1.05	2.01	Nitroglycerin 32μg/min.
3	CABG (4) EF .10 LVEDP 15	100/53	90/110/40	16	13	2.1	2.7	15	17	1205	853	.45	1.10	None
4	VA EF .05 LVEDP 25	105/60	90/120/40	25	20	2.0	3.0	10	22	2000	1866	.66	1.40	None
5	CABG (1) EF .21 LVEDP 25	?0/60	60/80/40	19	13	[illegible]	1.5	7	9	1?00	1117	—		Epinephrine 4μg/min Xylocaine 2 mg/min
	EF LVEDP													
x̄	.18 25	105/64	86/107/42	17	13	1.7	2.3	19	23	1763	1289	.74	1.63	
SE	.05 3.2	11.?/5.5	6.8/7.0/?.0	2.3	1.8	.3	.3	7.2	6.6	151	173	.13	.23	

P < .05 by Student's t test
1:8 = IABP on 1:8 mode 1:1 = IABP on 1:1 mode CABG = coronary artery bypass grafts VA = ventricular aneurysm

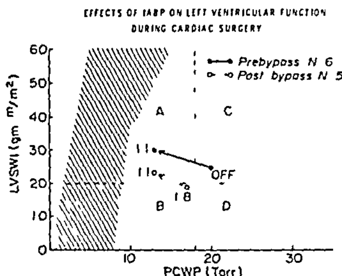


Fig 2 A left ventricular function diagram is shown with the normal range *shaded dark* The diagram is divided into the four "shock boxes as described by Bolooki and associates Box *A* has the best function and Box *D* has the worst The mean values of the six patients were studied before bypass began in Box *C* and moved to *A* with the IABP The post bypass patients moved from Box *B* on 1 8 to Box *A* on 1 1

(Table IV) Comparative measurements were made with the IABP on the 1 8 and 1 1 modes Two of the patients were still receiving catecholamines and one patient was receiving nitroglycerin The 1 1 mode of the IABP decreased SBP PCWP and TPR while it increased DBP CI LVSWI and the endocardial viability ratio (EVR)

Fig 2 shows the effect of the IABP on the Starling left ventricular function curve In both the pre bypass and post bypass groups of patients the curve was shifted up and to the left representing improved left ventricular function with the IABP However neither group of patients obtained normal left ventricular function (shaded area of the curve)

Discussion

The exact role of the IABP in cardiac surgical patients is still evolving but the incidence of its use appears to be decreasing from its peak in 1976 The frequency of use of the IABP varies widely from institution to institution and depends on the volume of surgery skill and speed of the surgical and anesthesia teams myocardial preservation techniques used during cardiopulmonary bypass, use of monitoring techniques and a thorough understanding of anesthetic and cardiac drugs

Preoperatively we primarily used the IABP to stabilize patients with complicated acute myocardial infarctions Bardet and colleagues [3] reported on the combined use of the IABP to stabilize 13 patients after an infarction and surgery to correct their associated mechanical defects such as ventricular septal defects [11] Twelve patients survived the surgery and eight survived for over one year We employed the IABP in 19 patients with mechanical problems or refractory shock following acute myocardial infarctions with similar results (84% survived the operation)

Balloon insertion in the operating room before cardiopulmonary bypass is its most controversial use We were very conservative in the use of the IABP at this time during surgery since we believe most patients can be safely anesthetized with the careful use of modern monitoring and anesthetic techniques and without the complications associated with the use of the IABP In Group II we used the IABP for patients with recent complicated infarctions who had not required the balloon preoperatively patients with chronic severe left ventricular dysfunction and one patient with severe coronary artery disease and idiopathic hypertrophic subaortic stenosis (IHSS) The decision whether to place the balloon prior to the induction of anesthesia or after the induction has to be individualized for each patient This was done by evaluating the patient s personality anxiety level ability to cooperate and hemodynamics while awake

Some authors have recommended the use of the IABP in the pre bypass period for all patients with (1) left main coronary artery disease (2) pre infarction or unstable angina or (3) moderately depressed left ventricular function We do not believe the IABP is necessary for these indications Garcia and associates reported on 18 patients who had left main coronary disease with excellent left ventricular function (lowest ejection fraction equaled 0 52) In their study 13 patients had the IABP procedure and had uneventful operations while two of five patients without the IABP had a cardiac arrest during the anesthetic induction Unfortunately the anesthetic and monitoring techniques were not described in detail In the past six years we have operated on 203 patients with left main coronary artery disease [11] Many of the patients had depressed left ventricular function The hospital mortality rate was under 3% and the perioperative infarction rate was only 3% The IABP was

used in only 1% of the patients (all after cardio pulmonary bypass) Therefore we believe the IABP is not needed in the vast majority of patients with left main coronary artery disease

Cooper and colleagues and Goldman and asso ciates have recommended the preoperative use of the IABP in all patients with unstable angina or moderate left ventricular dysfunction Unsta ble angina alone is not one of our criteria for the use of the IABP unless it follows an acute myocardial infarction The problem with using poor left ventricular function as a criterion for the balloon is that each author defines poor left ventricular function differently and measures left ventricular function using different techniques Cooper and associates reported six patients who received the IABP preoperatively due to poor left ventricular function The patients ejection frac tions ranged from 0 40 to 0 56 with an average of 0 50 Understandably all of these patients did well during surgery Goldman and co workers used an ejection fraction of less than 0 4 as their indication for the IABP while others have used 0 3 or less We have become less concerned with poor left ventricular function alone as a criterion for the pre bypass use of the IABP in coronary revascularization patients The reason for this is that we have seen many patients with very poor left ventricular function (ejection fraction < 0.3) undergo coronary revascularization without the IABP with minimal problems In 1977 only two patients received the IABP before bypass for poor left ventricular function One was in refractory pulmonary edema and one was in cardiogenic shock with an acute left ventricular aneurysm

Our indications for using the IABP following cardiopulmonary bypass have also undergone revision Improved anesthetic techniques myo cardial preservation and vasodilator therapy appear to have decreased the need for the IABP after bypass In the past too much use was made of vasoconstrictors alone in an effort to discontin ue cardiopulmonary bypass and the IABP was needed more often We believe the proper use of inotropes and vasodilators alone or in combina tions has served to reduce the need for the IABP after cardiopulmonary bypass

Serial hemodynamics have previously been reported in patients receiving balloon counterpul sation for cardiogenic shock Bolooki and co workers also reported the intraoperative hemo dynamic effects of the IABP in 35 patients He found the cardiac index increased by 30% end diastolic pressure decreased by 20% and diastolic blood pressure increased by 100% In the current study we found that the cardiac index increased by 16% pre bypass and 35% post bypass PCWP decreased by 35% pre bypass and by 24% post bypass and diastolic blood pressure increased by 90% pre bypass and 67% post bypass In addition the IABP decreased the TPR and increased the LVSWI both in the pre bypass and post bypass periods Thus the IABP decreased preload and afterload and improved left ventricular function in all the patients studied

Reported complications of the IABP have included ischemia of the leg dissection of the aorta thrombus formation and embolization thrombocytopenia infection and gas emboliza tion In this study the only complications seen were three cases of moderate ischemia of the leg two cases of thrombocytopenia and one superfi cial infection at the insertion site

In conclusion we believe the IABP can be extremely useful and life saving in certain cardiac surgical patients However it should be used selectively for specific indications especially in the pre bypass period It is not necessary to use the IABP prophylactically in patients with left main coronary artery disease unstable angina or decreased left ventricular function In these patients careful anesthetic management exten sive monitoring and appropriate pharmacological intervention can be used instead of the IABP In large part this accounts for our decreasing use of the IABP during cardiac surgery

Summary

The use of the intra aortic balloon pump (IABP) in cardiac surgical patients has become accepted treatment The purposes of this study were (1) to determine the frequency of use of the balloon (2) to re evaluate the indications for the IABP and (3) to assess the hemodynamic effects of the balloon during surgery

In the past 24 months the IABP was used in 63 of 1 738 (3 62%) adult cardiac surgical patients Eight patients required the IABP prior to surgery due to complicated acute myocardial infarctions In 13 patients the IABP was used in the oper ating room before bypass for complicated infarc tions or severe left ventricular dysfunction It was not considered necessary before bypass in patients with left main coronary artery disease moderately depressed left ventricular function or unstable angina In addition 42 patients required

the IABP to discontinue cardiopulmonary bypass

Detailed hemodynamic measurements were made in 11 patients. The IABP decreased systolic blood pressure, left and right ventricular filling pressures, and peripheral resistance, while it increased diastolic and mean arterial pressures, stroke work, cardiac output, and the endocardial viability ratio. The intra-aortic balloon was shown to be life-saving in certain patients. However, it should only be used selectively for specific indications. Careful surgical and anesthetic management with good monitoring can be used in many patients instead of the balloon.

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Complications with retained transvenous pacemaker electrodes

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In permanent cardiac pacing irreversible loss of function of the transvenous electrode catheter eventually requires insertion of a new lead this may be due to electrode displacement exit and/or entrance block lead fracture and insulation defects Similarly infections of the pacemaker system may make removal of the intracardiac lead inevitable In this situation it is sometimes found that the defective electrode cannot be withdrawn from the cardiovascular system because it has become firmly enclosed by fibrous tissue along its course from the vein tract to the right ventricle This is particularly true when enlarged tips are used in order to evoke a safe attachment to the right ventricular apex Under such circumstances the old electrode catheter is usually left in situ after being severed and sutured at its entrance into the venous system This report based upon years experience with permanent cardiac pacemakers illustrates the risks and complications of this practice

Methods

A retrospective study was done reviewing the clinical records on all patients who had a permanent transvenous pacemaker inserted from 1964 to 1976 Using a specially designed computerized documentation system the data of a total from 1 734 pacemaker patients (53 5% males 46 5% females mean age 69 years) were reviewed with particular reference to complications requiring corrective interventions The data presented are based on a follow up by the end of June 1977

Of a total of 721 surgical procedures for various complications (including pulse generator exhaustion) 331 were necessary for electrode failure In 124 patients a new lead had to be inserted Among these there were 46 patients (24 males 22 females) ranging in age from 8 to 86 years (average 64 5 years) in whom failing transvenous electrodes could not be removed and had to be left in situ These patients form the basis of the present report Attempts at forceful or prolonged traction as proposed by various authors were generally not made (vide infra)

Results

The individual clinical data of the study population are presented in Table I and Table II summarizes the follow up results

From 1964 to November 1970 328 pacemaker patients had electrode catheters with smooth tips inserted (Elema EMT 588 Biotronik first model Biotronik IE 60) During this period 17 functionless electrode wires (5 2%) were left within the heart From November 1970 only electrodes with a conical shoulder at their tip (Biotronik IF 60 K IE 60 K 10) were used in 1 406 patients among these 29 functionless leads were left in the heart (2 1%)

Non infectious complications In 25 patients the retained electrodes had failed as a consequence of non infectious conditions These were exit block due to threshold increases in nine electrode displacement in nine and lead fracture

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Table 1 Clinical data

Pt	Age/ Sex	Clinical diagnosis	ECG at time of implantation	Type of pacemaker	Type of electrode	Date of initial insertion	Follow up
A No infection							
1	69/F	Id sync	Intermitt AVB II/2	Elema EM 139	Elema EMT 588	3/1/66	4/11/76—New lead (displacement) alive no complications
2	70/F	Id Sync	CHB	Elema EM 139	Elema EMT 588	25/2/66	8/5/70—New lead (exit block) alive no complications
3	84/M	CAD Sync	CHB	Biotronik II 3	Biotronik first model	7/3/68	29/6/76—New lead (lead fracture) alive no complications
4	69/F	Id Sync	CHB	Biotronik II 3	Biotronik IE 60	7/6/68	2 /1/7?—New lead (displacement) 6/75—died of cancer
5	12/F	VSD Sync	CHB (postop)	Biotronik II 44 90	Biotronik IE 60	8/9/68	7/3/77—New lead (exit block) alive no complications
6	49/F	SSS	SB	Biotronik IRP 44	Biotronik IE 60	10/4/70	23/12/74—new lead (displacement) alive no complications
	55/M	CAD SSS Sync	SB	Biotronik IRP 44	Biotronik IE 60	27/7/70	Five reoperations for displacement 14/11/72—new lead 12/72—died of catheter embolism (see case report)
8	35/M	Postmyocarditis	CHB	Biotronik IRP 44	Biotronik IE 60 K	16/4/71	11/1/74—New lead (exit block) alive no complications
9	9/M	Congenital Sync	CHB	Biotronik IRP 44 90	Biotronik IE 60 K	18/8/71	25/6/76—New lead (body growth) alive occasionally exit block
10	51/M	Id Sync	SB AVB II/2	Biotronik IRP 44	Biotronik IE 60 K	7/9/71	2_/1/73—New lead (displacement) 1/76—died of polyneuropathy
11	64/F	MVD CHF	Atr fib CHB	Biotronik IRP 44	Biotronik IE 60 K	1/9/72	12/9/72—New lead (displacement) 10/74—died of CHF
12	5/M	Id Sync	CHB	Biotronik IRP 44	Biotronik IE 60 K	27/10/7?	7/6/74—New lead (lead fracture) 6/76—died of uremia
13	82/F	CAD CHF	Atr fib	Biotronik II 45	Biotronik IE 60 K	5/1/73	26/2/74—New lead (exit block) ?/75—died of CHF
14	64/F	CAD CHF	AVB II/2 intermitt CHB	Biotronik IRP 44	Biotronik IE 60 K	30/1/73	12/8/75—New lead (lead fracture) alive no complications
15	83/M	CAD CHF Sync	RBBB + LAH intermitt CHB	Biotronik IRP 44	Biotronik IE 60 K	1/6/73	2/4/74—New lead (lead fracture) alive no complications
16	58/F	CAD SSS	SB SAB	Biotronik IRP 44	Biotronik IE 60 K	29/11/74	8/7/75—New lead (exit block) alive no complications
17	50/M	Id Sync	RBBB + LAH Intermitt CHB	Biotronik IRP 44	Biotronik IE 60 K	20/2/74	28/5/76—New lead (lead fracture) alive occasionally exit block
18	61/F	Id Syn	CHB	Biotronik IRP 44	Biotronik IE 60 K 10	16/8/74	3/6/76—New lead (displacement) alive no complications
19	84/M	CAD CHF	Atr fib	Biotronik IDP 54	Biotronik IE 60 K	4/11/74	24/1/75—New lead (lead fracture) alive no complications
20	8/M	Tetralogy of Fallot	CHB (postop)	Biotronik IDP 44	Biotronik IE 60 K	20/12/74	15/6/76—New lead (exit block) alive no complications

Abbreviations Atr fib = atrial fibrillation AVB = atrioventricular block CAD = coronary artery disease CHB = complete heart block CHF = congestive heart failure Id = idiopathic sclerodegenerative disease of the conduction system IVC = inferior vena cava LAH = left anterior hemiblock MVD = mitral valve disease PSVT = paroxysmal supraventricular tachycardia RA = right atrium RBBB = right bundle branch block SB = sinus bradycardia SSS = sick sinus syndrome Sync = syncopes VSD = ventricular septal defect

Table I Cont d

Pt	Age/Sex	Clinical diagnosis	ECG at time of implantation	Type of pacemaker	Type of electrode	Date of initial insertion	Follow up
A No infection (cont.)							
21	65/F	CAD CHF Sync	CHB	Biotronik IRP 41	Biotronik IE 60 K 10	14/2/75	14/10/ 5—New lead (exit block) 1/76—died of CHF
22	76/F	CAD Sync	SB AVB II/2	Biotronik IDP 54	Biotronik IE 60 K 10	16/1/ 6	23/12/76—New lead (displacement) alive no complications
23	5/F	CAD CHF Sync	CHB	Biotronik IDP 54	Biotronik IE 60 K 10	20/1/ 6	5/1/77—New lead (displacement) alive no complications
24	68/M	MVD CHF	Atr fib	Biotronik IDP 54	Biotronik IE 60 K 10	8/3/ 6	5/9/76—New lead (exit block) alive no complications
25	54/F	Id Sync	CHB	Biotronik IDP 54	Biotronik IE 60 K 10	3/12/76	29/?/ 6—New lead (exit block) alive no complications
B Infection							
26	66/F	CHD CHF Sync	CHB	Elema EM 139	Elema EMT 88	21/4/66	13/9/67—New lead 12/67—died of cerebral hemorrhage
27	75/M	CHD CHF Sync.	CHB	Biotronik IP 44	Biotronik IE 60	15/8/66	8/5/70—New lead 1/ 4—died of septicemia
28	86/M	CAD Sync	CHB	Elema EM 142	Elema EMT 588	28/3/67	25/5/76—New lead 6/76—died of septicemia
29	72/F	MVD CHF	Atr fib	Biotronik IRP 3	Elema EMT 588	18/ /68	24/8/ 1—New lead infection not healed until functionless lead migrated into RA alive
30	86/F	CAD Sync	CHB	Biotronik IP 3	Biotronik first model	20/9/68	5/10/ 1—New lead lost from follow up
31	65/F	Id Sync	CHB	Biotronik IP 44	Biotronik IE 60	16/6/69	23/8/ 4—New lead infection persists despite repetitive surgery thoracotomy considered
32	69/M	SSS Sync.	SB PSVT	Biotronik IRP 44	Biotronik IE 60	17/12/69	9/8/74—New lead alive infection healed
33	68/M	CAD CHF	Atr fib	Biotronik IRP 44	Biotronik IE 60	19/5/70	26/11/76—New lead, lost from follow up
34	77/F	Hypertensive heart dis CHF	Atr fib	Biotronik IRP 44	Biotronik IE 60	9/8/ 0	28/1/72—New lead infection healed 5/74—died of CHF
35	25/M	Ostium primum defect	CHB (postop)	Biotronik IRP 44	Biotronik IE 60	2/9/70	5/8/ 6—New lead alive infection persists despite repetitive surgery thoracotomy considered
36	60/M	CAD CHF	CHB	Biotronik IRP 44	Biotronik IE 60 K	21/4/71	28/6/ 4—New lead alive infection healed
37	84/M	CAD Sync	CHB	Biotronik IRP 44	Biotronik IE 60 K	7/5/71	30/7/71—New lead lost from follow up
38	75/M	CAD Sync	CHB	Biotronik IP 44	Biotronik IE 60K	28/1/72	15/5/72—New lead alive infection healed
39	72/M	CAD CHF Sync	CHB	Biotronik IP 44	Biotronik IE 60 K	21/4/72	17/2/76—New lead alive infection healed
40	9/M	CAD CHF Sync	CHB	Biotronik IP 44	Biotronik IE 60 K	16/6/72	18/8/74—New lead alive infection healed

continued

Table I Cont'd

Pt	Age/Sex	Clinical diagnosis	ECG at time of implantation	Type of pacemaker	Type of electrode	Date of initial insertion	Follow-up
B Infection (cont)							
[illegible]	[illegible] M	CAD CHF	CHB	Biotronik IRP 44	Biotronik IF 60 K	8/12/72	[illegible]—New lead alive infection healed
[illegible]	[illegible]/F	CAD Sync	CHB	Biotronik [illegible] 44	Biotronik IF 60 K	[illegible]	[illegible]—New lead alive infection healed
43	[illegible] F	CAD CHF	RBBB + LAH AVB I	Biotronik IRP 44	Biotronik IF 60 K 10	[illegible]/12/74	14/8/7[illegible]—New lead [illegible]—died of septicemia
44	[illegible] M	CAD CHF Sync	CHB	Biotronik IDI [illegible]	Biotronik IF 60 K 10	18/3 [illegible]	21/[illegible]—New lead infection persisted functionless lead migrated to IVC [illegible]—died of septic pulmonary emboli
[illegible]	[illegible] M	Hypertensive heart dis CHF	Atr fib	Biotronik IDP 54	Biotronik IF 60 K 10	18/7/[illegible]	19/3/76—New lead lost from follow up
46	[illegible] F	MVD Sync	Atr fib	Biotronik IDI [illegible]	Biotronik IF 60 K 10	2[illegible]/2/76	18/5/76—New lead alive infection healed

Table II Patients studied with retained electrode catheters

	Fate of functionless electrode		N = 46
[illegible]	infected	25	not infected
11	infections healed (2 deaths not pacemaker related)	24	without complication (6 deaths not pacemaker related)
4	lost from follow up infection persists	1	death due to catheter embolism into pulmonary arterial system
4	deaths due to septic complications		

in six instances In addition a child who had his first transvenous pacemaker inserted at the age of three for syncope due to congenital complete heart block received a second electrode wire 5 years later after the original lead had become too short due to body growth

Apart from one patient to be described in detail no complications thus far have been provoked by the presence of a non infected electrode retained within the cardiovascular system over a follow up period ranging from 3 to 86 (mean 21 4) months Tricuspid insufficiency has never been noted Three patients succumbed to their primary cardiac disorder and three to other diseases unrelated to pacemaker therapy

Case report (patient No 7) This 55 year old man with a history of anterior myocardial infarction in 1967 and recurrent deep thrombosis of the lower extremities developed sinus node dysfunction with marked sinus bradycardia and fainting episodes In July 1970 he underwent implant of an R wave triggered transvenous pacemaker type Biotronik IRP 44 Up to November 1972 a total of five reoperations for episodes of exit block were performed with repositioning of the intracardiac lead After pacing had ceased again a new electrode was inserted on November 14 1972 The old electrode was withdrawn but could not be pulled out beyond the superior vena cava It was therefore severed at its entrance into the right cephalic vein and was secured with sutures (Fig 1A) Pacing resumed and remained consistent On November 17 a chest roentgenogram disclosed that the proximal stump had freed itself and had



Fig. 1A through C. *A*, Inactive pacemaker electrode with its tip in the superior vena cava. *B*, The electrode catheter has freed itself and has drifted to the inferior vena cava; the proximal stump is visible in the superior vena cava. *C*, The catheter has migrated into the pulmonary arterial system.

drifted to the superior vena cava (Fig. 1*B*). Three days later the catheter was found forming a loop in the pulmonary arterial system with its proximal and distal ends in the main branches of the left pulmonary artery (Fig. 1*C*). Thoracotomy, which was suggested to the patient, was refused. Five days after hospital discharge he died suddenly at home; autopsy was not performed.

Infectious complications. There were 21 retained electrode catheters associated with infection of the pacemaker system. Infection was almost exclusively secondary to skin erosions over the pulse generator, the first signs of local inflammation being observed not earlier than 30 days after surgery when impending or manifest ulceration was present. Only in two instances did infection seem to be directly related to preceding surgery. Skin erosion over the electrode was not observed in this series and does not play a significant role at our institution, since we choose the transcephalic approach of catheter insertion whenever possible.

In 11 instances eradication of infection could be achieved by surgical management including removal of the pulse generator and the subcutaneous portion of the electrode catheter, cutting, burying and securing the retained catheter, and drainage in combination with local and systemic antibiotic treatment. In this group there is one woman in whom infection did not heal until the catheter fragment, which was retained in the superior vena cava, migrated into the right atrium. Since then it has been coiled up there for five years without any adverse reaction. Her poor clinical condition percludes thoracotomy. In six patients infection could not be controlled despite repetitive surgical interventions and antibiotic treatment. While infection still persists in two individuals in whom thoracotomy is being considered, four patients died from septicemia, including one patient whose death was caused by septic pulmonary emboli deriving from infected thrombus formation around a catheter which had migrated into the inferior vena cava. Of these four fatal cases, operative removal of the retained catheter fragment was refused by one; in one patient an emergency operation was precluded by his poor clinical condition, while in two subjects the correct therapeutic decision was not made in time. Two patients' deaths were not pacemaker related. If one eliminates four individuals lost from follow-up, a mortality rate of 23.5% (four of 17 patients) can be calculated when electrode catheters were retained while infection was present. In six instances of persistent infection an even higher mortality rate (four of six patients) was encountered. Similarly, the migration of a proximally severed electrode, whether infected or not, was a fatal complication in two out of three cases.

Discussion

The presence of a transvenous electrode catheter within the cardiovascular system provokes a fibrous endothelial reaction which forms a kind of "neo-endothelium" around the catheter along its course within the vein tract and the heart. The reaction lodges the electrode catheter more firmly in the right ventricular trabeculae and renders its withdrawal difficult or even impossible. This is

particularly the case with silicone rubber or polyethylene catheters that are known to encourage a fairly prominent endothelial reaction [1] Electrodes with enlarged tips are more likely to get firmly trapped in the right ventricular wall [4] although in the present patient series trapping was also observed with smooth tipped catheters In general removal from the cardiovascular system becomes difficult after about six to eight weeks following insertion

Several techniques of prolonged continued traction have been proposed by various authors whereby trapped electrodes might be successfully removed Severe complications however have been reported with forceful and prolonged traction These complications include arrhythmias with shock concomitantly with fluoroscopically visible invagination of the right ventricular wall to the tricuspid valve ventricular tachycardia ventricular fibrillation [7] intracardiac lead rupture and arteriovenous fistula to the internal jugular vein In addition Tallury and co workers described lethal hemopericardium due to a 2 cm tear in the right ventricular apex after a too forceful traction Kohler and Schmitt extracted torn parts of the tricuspid valve with adjacent chordal and myocardial tissue during a similar procedure In view of these risks many authors are reluctant to use prolonged or forceful traction and it is because of our agreement with these objections that we have generally made no similar attempts at traction

This policy seems particularly justified for retained electrodes without accompanying infection since the results of this study have revealed that non infected functionless leads can be left in situ over many years without causing any functional abnormalities In particular tricuspid insufficiency which some investigators feel is a real danger was not observed In addition pathologic anatomic observations by Lagergren and colleagues have shown insignificant changes after several years of pacing Prolonged traction may convert a closed uncontaminated electrode system to an infected one

Thoracotomy has been performed to remove the inactive electrode according to the surgical principle that functionless foreign material be generally removed from the body The uneventful course however that we have observed when no infection of the retained electrode was present has prompted us not to follow this principle which would impose a serious risk to most of the elderly pacemaker patients

The only complication that we encountered with non infected retained electrodes cannot be attributed to a failure of this policy The detachment of a proximally severed and sutured lead and its subsequent migration is a rare event (one out of 25 instances in the present series) provided no infection is present and we believe that inadequate fixation of the electrode stump at its venous entrance during operation was responsible for the complications encountered in the one patient Therefore care should always be taken to provide a reliable proximal fixation of the stump

Loosening of securing sutures cannot always be prevented if local infection is present and we have observed two further cases of catheter migration with detachment of the proximal stump from the infected tissue In one patient infection healed after the catheter had freed itself from its fixation and had coiled up within the right atrium The other patient died from septic pulmonary emboli originating from thrombus formation around a catheter which had migrated into the inferior vena cava Thus of the three cases of migration of catheter electrodes in our series two were fatal

While embolization of polyethylene catheter fragments into the pulmonary vascular bed does not seem to be so rare an event [1] electrode catheters because of their partially metallic nature and hence higher specific gravity have almost exclusively been observed to migrate into the lower half of the body such as the inferior vena cava or the hepatic venous system Perhaps the body position at the moment of migration plays a role in determining the site of embolization The case of pulmonary embolization of an electrode catheter is exceptional in this respect and we have been able to find only one similar previous report [8]

Although the sudden death in our case remains unexplained it is likely that it is related in some way to the catheter embolization

Experiences from the literature similar to ours underline the necessity to remove migrated electrode catheter fragments Out of four patients in whom the embolized fragment was left one died whereas the remainder of patients reported on with this complication survived after having

their catheter extracted[4, 10, 13] Additional reports on embolized polyethylene catheters and foreign bodies in general[3] confirm the high risk without surgical management Transvenous extraction of electrode catheters may be successful- If however such a procedure fails operation (if necessary thoracotomy) is required

In agreement with other investigators[6] we observed infections of the pacemaker system predominantly secondary to skin ulceration over the pulse generator and these pose a serious threat to the patient Local and/or systemic antibiotic therapy alone in our and other authors experience is generally not successful except when skin erosion has not yet been followed by infection and aseptic inflammation is still present In 11 out of 21 patients of our series local procedures proved successful in eradicating local infection If however infection reaches the vascular system serious complications may be encountered unless the electrode catheter is removed Thus fatal infective endocarditis[31] as well as septicemia[6, 3, 2, 33] has been reported due to infected endocardial electrodes Furthermore a chronic local fistula may develop and may facilitate detachment of securing sutures at the venous entrance followed by potentially fatal catheter embolization In 17 similar situations we have experienced four deaths due to septicemia including one event of catheter embolization and septic pulmonary embolism If therefore chronic infection persists despite adequate local surgical and antibiotic treatment we believe thoracotomy to be indicated whenever the patient s condition permits operation

Summary

Out of a series of 1 734 pacemaker patients the clinical course of 46 patients was reviewed in whom a functionless endocardial electrode was retained Non infected electrodes (25 patients) were generally well tolerated without complications except in one patient who experienced fatal catheter embolism into the pulmonary artery In cases of infected electrodes (21 patients) a mortality rate of 25% was encountered due to septic complications Catheter migration was fatal in two out of three patients It is concluded that entrapped electrode catheters should be removed by thoracotomy if persisting infection is present or if catheter migration has occurred

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Demonstration of re-entry within the canine specialized conduction system

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The precise mechanism of most ventricular arrhythmias in the clinical setting remains unknown Enhanced automaticity or re entry are the most commonly thought of etiologies for ventricular arrhythmias The basic requirements for any re entry circuit are most simply—two or more pathways of conduction temporary block of conduction in one pathway and slow conduction in the other pathway The circuit time in the re entrant pathway must exceed the recovery time of any tissue within the re entry circuit Several models of re entry within the ventricular myocardium have been reported The methods of facilitating slow conduction in these models included myocardial cooling[1 2] premature stimuli,[3] myocardial ischemia [2] and elevation of potassium and catecholamines in isolated Purkinje tissue[13 4]

The specialized conduction system has frequently been suggested as a possible site for the occurrence of some re entrant arrhythmias The bundle branches have several anatomic and physiologic characteristics that make them a likely location for re entrant impulses Their long length which has been estimated to 8 0 cm in man from distal right bundle to shorter fascicle of the left bundle[15] minimizes the need for extremely slow conduction In addition the bundle branches are wrapped in a connective tissue sheath that serves to electrically insulate them from surrounding myocardium[16] The limited points of entry and exit of electrical impulses from the bundle branches serve to ensure that the full length of the specialized conduction system is available for use in re entrant circuits and also acts to limit the variety of possible re entrant circuits within the specialized conduction system

Re entry circuits utilizing the bundle branches have frequently been proposed[17 23] but are not well verified In the present study simultaneous electrograms were recorded from the major portions of the specialized conduction system The activation sequence within the specialized conduction system was mapped during induced re entry It was demonstrated that the re entrant circuit was within the specialized conduction system

Methods

This study is compiled from observations made during 19 acute canine experiments in which electrophysiologic and hemodynamic stability allowed repetitive initiation of re entry beats and demonstration of the activation sequence within the specialized conduction system Mongrel dogs weighing 15 to 35 kilograms were anesthetized with 30 mg/kg of phenobarbital Artificial ventilation was achieved through a tracheostomy with a Harvard ventilator adjusted according to the Kleinman and Radford nomogram[24] Body temperature was supported by a DC heating pad Arterial and venous pressures were monitored throughout the experiment and volume replacement was used to maintain a physiologic blood pressure The heart was exposed using a midline

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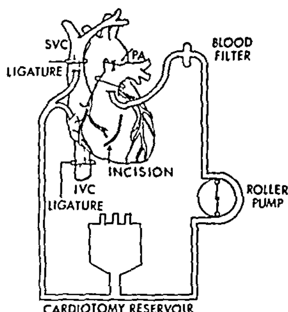


Fig 1 Right heart bypass system Blood was diverted with snare ligatures from superior and inferior venae cavae into a cardiotomy reservoir A roller pump was used to pass the blood through a filter and into the pulmonary artery The location of the incision in the right ventricular anterior wall is shown

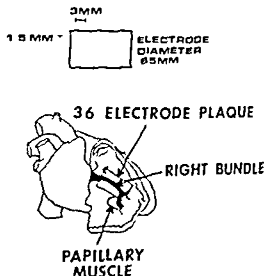


Fig 2 Placement of 36 electrode plaque This diagram shows a lateral view of the heart opened to show the right septal surface containing the right bundle branch The approximate position of the electrode plaque is shown and is also described in the text The dimensions of the plaque and arrangement of electrodes are shown *at the top of the figure* Subsequent illustrations will refer to electrodes Rb to Rb, Rb represents the most proximal and Rb the most distal pair of electrodes overlying the right bundle

sternal incision The animals were each given 10 000 units of heparin and the right heart was bypassed as shown in Fig 1 The superior vena cava was cannulated via the azygos vein and the inferior vena cava was cannulated through the right atrial appendage Blood from the superior and the inferior venae cavae was collected in a cardiotomy reservoir A roller pump was used to return the blood to the pulmonary artery after passing it through a filter Occlusion of the superior and inferior venae cavae and pulmonary artery with umbilical tapes allowed diversion of blood into the right heart bypass system Small suction drains were placed in the right atrium and right ventricle to remove coronary venous blood and return it to the cardiotomy reservoir The pump system was primed with 0 5 to 0 7 liters of normal saline With the animal on right heart bypass a 2 to 3 cm curvilinear incision was made in the anterior wall of the now empty right ventricle to expose the septum containing the right bundle branch A 10 × 15 mm plaque with 36 stainless steel electrodes flush to its surface was sutured over the right bundle The poles of each electrode pair were separated by 1 5 mm The plaque was placed lateral and inferior to the small papillary muscle that inserts into the pulmonary conus and was superior and medial to the anterior papillary muscle (Fig 2) Pairs of electrodes from which electrograms with the greatest amplitude were obtained were selected for recording and to include sites of the proximal and distal right bundle Bipolar plunge electrodes made of stainless steel Teflon coated 007 inch diameter wire were placed on the proximal left bundle Placement was achieved by inserting the wires through a No 20 gauge needle and plunging the needle into the right septal surface 5 mm to either side of the proximal right bundle branch The needle was then withdrawn over the electrode wires After placement of electrodes the incision in the right ventricular wall was closed and the right heart bypass was discontinued Additional plunge electrodes were then inserted into the right and left ventricular apices for endocardial pacing and recording The positions of all the electrodes were confirmed at the completion of the experiment by iodine staining of the specialized conduction system Bipolar catheter electrodes were used to record from the His bundle and middle portion of the left bundle The poles of the catheter electrodes were 2 mm wide platinum bands separated by 2 mm One catheter was placed in the aortic root and the other was placed in the cavity of the left ventricle With two or more electrodes on each bundle

branch there was no need to use the change in polarity of an extracellular electrogram to infer a change in activation sequence [5] All electrograms were recorded with a frequency response of 50 to 2 000 Hz ECG Lead II and sometimes Lead I were recorded at a frequency response of 0 2 to 2 000 Hz Recordings were made on a light beam oscillograph at paper speeds of 25 to 200 cm /sec The sinus node was crushed to allow control of drive at long cycle lengths Bipolar hook elec trodes were attached to the right atrial appen *dage for stimulation and for recording atrial* electrograms Stimuli of 2 msec duration and at 1.5 times threshold were used for cardiac stimu lation Re entry was induced by premature stim ulation of the right ventricle In all the prepara tions included in this study placement of elec trodes on the specialized conduction system did not change the activation time from His bundle to right and left ventricular apices This was taken as evidence that the electrode placement did not functionally injure the specialized conduction system

In some experiments an area of epicardial tissue was cooled by circulating a 10 to 15° C solution through a loop 1 5 cm across formed from glass tubing and sutured to the anterior surface of the left ventricle A second area on the anterior wall of the right ventricle was warmed by circulating a 40 to 50 C solution through a similar glass loop *Re entry was produced by* giving premature stimuli to a right ventricular site in close proximity to the warmed epicardium This method was used by Geddes and associates to modify recovery times and conduction velocity in studies designed to simulate the electrophysio logic changes associated with acute ischemia We utilized this model in 15 additional experiments to see if there was facilitation of re entrant impulses

In 10 additional dogs (without recording made from the specialized conduction system) surgical section of the right bundle was performed to observe its effects on the previously elicited re entrant excitation The right bundle was sectioned by inserting a needle through the ante rior right ventricular wall and moving it across the right septal surface until right bundle branch block was observed on the monitored ECG leads In seven other dogs with multiple electrodes on the specialized conduction system reversible conduction block in the right bundle was induced by long duration anodal currents of 0 1 to 0 6 ma

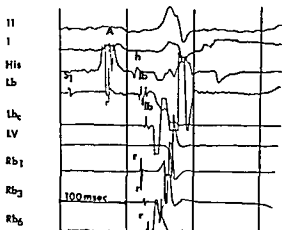


Fig 3 Activation sequence during right atrial drive at a 400 msec basic cycle length *II* and *I* refer to ECG limb leads. *LB* refers to proximal left bundle electrogram *Lbc* refers to the electrogram recorded by catheter electrodes over the middle portion of left bundle *LV* refers to electrograms recorded from endocardium of the left ventricular apex *Rb* Rb_{3} and *Rb* refer to recordings from the proximal middle and distal electrodes respectively on the electrode plaque positioned over the right bundle *A* refers to the atrial pike on the His bundle electrograms *h* is His bundle activation *lb* indicates left bundle deflection *r* indicates right bundle activation and *S* refers to the stimulus artifact The same abbreviations are used in subsequent illustrations.

intensity applied to one of the electrodes overly ing the right bundle A large diameter (1 5 cm) chlorided silver electrode was placed in the subcu taneous tissue of the right leg to serve as the remote cathode

Results

Simultaneous recording of seven to 10 electro grams allowed for a reasonably detailed definition of the activation sequence within the specialized conduction system Fig 3 shows the activation sequence within the specialized conduction system during supraventricular drive This repre sents the most detailed in vivo simultaneous recording of activation within the specialized conduction system yet reported Following right atrial stimulation the His bundle was activated 40 msec after low left atrial activation The proximal right and proximal left bundles were simultaneously activated 8 msec after His bundle activation The earliest recorded ventricular acti vation occurred 27 msec following His bundle activation Propagation down the bundle branches to the ventricle was best demonstrated in the electrograms from the right side of

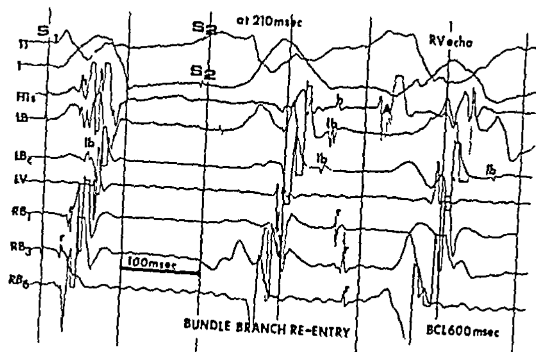


Fig 4 Bundle branch re-entry S represents the last of 9 regular stimuli delivered to the right ventricular apex at 600 msec cycle lengths Note that with regular drive of the right ventricular apex there is prompt retrograde activation of the right bundle branch preceding the myocardial activation near the electrode In contrast, premature stimulation as seen in the second complex fails to show activation of the specialized conduction system prior to activation of myocardium Note the late activation of the distal left bundle branch was followed by activation of the proximal left bundle branch His bundle proximal right bundle middle right bundle distal right bundle branch and then by the re-excitation of the right ventricular myocardium The potential for this re-entrant circuit to continue is shown by the late retrograde activation of the distal left bundle following the right ventricular echo complex

heart As seen in Fig 3 activation in the right bundle proceeded from base to apex and activation of the right septal myocardium began nearest the distal electrodes and propagated from apex to base Fig 3 also shows that the left bundle was activated in a base to apex direction Activation of the ventricle near the middle portion of the septum (mid left bundle electrode) preceded activation of the upper septum (proximal left bundle electrode)

While the specialized conduction system is likely to provide conduction pathways for many different re entrant circuits our study involved only re entrant circuits produced by premature stimulation of the right ventricle

Fig 4 shows the activation sequence within the specialized conduction system during regular right ventricular drive and also the activation sequence during premature right ventricular stimulation The first complex in Fig 4 resulted from the last of nine regular stimuli at 600 msec intervals There is prompt retrograde activation of the right bundle branch that causes activation of the His bundle and antegrade activation of the left bundle branch as one of us has previously reported [16] In contrast the second complex shown in Fig 4 is the result of a premature stimulus to the right ventricle which fails to cause retrograde activation in the right bundle branch There is however slow right to left myocardial activation which results in late retrograde activation of the distal left bundle followed in turn by the activation of the proximal left bundle His bundle and right bundle branch The antegrade activation in the right bundle branch is able to conduct across the site of previous conduction block and activate the right ventricular myocardium to produce a re entrant complex The activation sequence of retrograde conduction in the left bundle and antegrade conduction in the right bundle is shown in Fig 4 The sites of probable slow conduction must be between the right ventricular apical activation and the activation of the distal left bundle branch and also between the activation of the distal right bundle and the re excitation of the right ventricular myocardium The

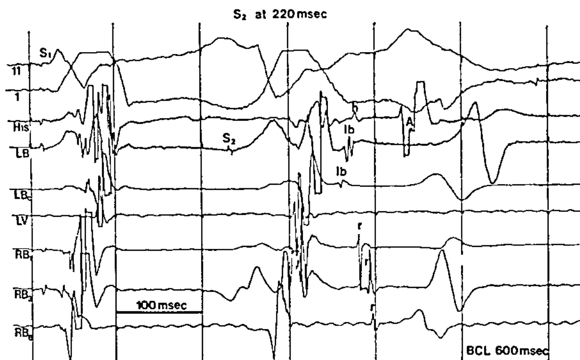


Fig 5 This tracing shows activation data from the same experiment as shown in *Fig 4* The premature stimulus is given 10 msec less prematurely as compared to *Fig 4* In this instance the activation is nearly identical to that seen in *Fig 4* except that there is failure to re excite the right ventricle after activation has proceeded antegradely down to the level of the distal right bundle branch

re entrant impulse causes re activation of the right ventricle after an interval of 165 msec The refractory period of the right ventricle at 600 msec cycle lengths was usually 190 to 230 msec in these experiments

Figs 5 and 6 show the effect of less premature stimuli to the right ventricular apex on the activation sequence in the bundle branches In Fig 5 the stimulus is only 10 msec less premature than that shown in Fig 4 The delay in activation of the left and right bundles is similar to that seen in Fig 4 However the impulse was unable to conduct across the site of previous conduction block to re activate the right ventricle Fig 6 shows the activation sequence in the bundle branches in response to a much less premature stimulus The stimulus to the right ventricle fails to activate the right bundle branch retrogradely and activates the distal left bundle and His bundle with much less delay causing their activation to be lost in the myocardial activation complexes The activation of the proximal right bundle electrogram is clearly shown with much less delay as compared to Figs 4 and 5 The impulse in this case fails to conduct beyond the proximal right bundle branch and thus fails to cause a re entrant complex

After the occurrence of one re entrant complex one might expect re-entry to continue We have observed two loops of re entrant activation within the bundle branches but have not yet been able to produce runs of tachycardias in any of these experiments

To prove that the activation sequence as seen in Fig 4 was responsible for the re entrant complex and that this phenomenon was not due to local re entry near the stimulus site as suggested by Castellanos and colleagues [7] we blocked conduction in the right bundle and observed the effect on the expected re entrant responses Conduction was blocked either by surgical section of the right bundle or by delivering long duration anodal blocking currents to the proximal right bundle With the latter method the conduction block was reversible With either method of conduction block of the right bundle re entrant beats did not occur in response to premature stimuli that previously resulted in a re entrant response

Geddes and co workers found in the presence

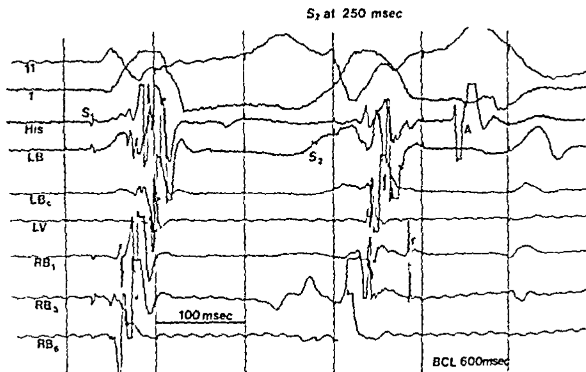


Fig 6. Shows the effect of a much less premature stimulus given to the right ventricular apex from the same experiment as shown in *Figs 4 and 5*. The premature stimulus, even though quite late, still failed to retrogradely activate the right bundle branch. The delay in retrograde activation of the left bundle and His bundle is much less and their activation is simultaneous with the myocardial activation. However, the antegrade activation of the proximal right bundle is seen and occurs with much less delay than in *Figs 4* and *5*. The antegrade activation in the right bundle failed to conduct to the middle portion to the right bundle branch and functioned to interrupt the re-entrant circuit.

of local cooling of the left ventricular epicardium and local warming of the right ventricular epicardium that premature stimulation of the right ventricle resulted in two types of re-entrant beats. One type of re-entrant beat appeared to be of left ventricular origin and the other of right ventricular origin. The re-entrant beats of right ventricular origin were thought to involve conduction paths within the specialized conduction system. Additional experiments were done in 10 dogs to further define the role of the specialized conduction system in re-entrant beats in the Geddes re-entry model. We found that surgical section of the right bundle terminated re-entrant responses of right ventricular origin but had no effect on the re-entrant response of left ventricular origin. Two additional experiments were done in which electrograms from the major portion of the specialized conduction system were recorded and it was documented that re-entry occurred within the bundle branches as seen in Fig 4 to cause the re-entrant beats of right ventricular origin. Epicardial warming of the right ventricle near the site of stimulation shortened right ventricular refractory periods by 30 to 40 msec and increased the echo window or the interval during which premature beats initiated re-entry responses from 10 to 15 msec to 30 to 40 msec. The re-entrant beats of left ventricular origin were not associated with activation of the bundle branches and were considered to be due to slow conduction in the cooled myocardium as reported by Wallace and Mignone.

Discussion

Re-entry has frequently been suggested as a mechanism for recurrent ventricular tachycardia in patients. Wellens and co-workers reported that they could terminate and initiate ventricular tachycardia by programmed stimulation methods in more than half of their patients with recurrent ventricular tachycardias. They suggested this as evidence that these tachycardias were due to a re-entry mechanism. Spurrell, Sowton and Deuchar[36] noted that ventricular premature beats induced during a ventricular tachycardia may alter the form and rate of

ventricular tachycardia without terminating it They suggested this was evidence of a long re entry pathway probably within the specialized conduction system They postulated that when block occurred in one conduction pathway the re-entrant impulse propagated through another pathway of different length within the specialized conduction system In two patients with recurrent ventricular tachycardia that they considered secondary to bundle branch re entry the left anterior fascicle was cut to divide the re entry pathway in an effort to terminate the arrhythmias In contrast Josephson and associates have convincing evidence that a large re entrant circuit is not responsible for most cases of ventricular tachycardia in man

Documentation of bundle branch re entry has not been conclusively demonstrated before although there has been considerable supportive evidence for its occurrence Moe and co workers[7, 15] proposed but did not document that functional right bundle branch block was associated with conduction proceeding down the left bundle followed by retrograde activation of the right bundle Moe and colleagues and later Zipes[19] were able to produce His bundle echo responses following premature supraventricular stimulation that caused functional right bundle branch block These workers proposed that the mechanism of the His bundle echo was re entry involving the bundle branches

Re-entry due to unidirectional block at the right ventricular Purkinje-muscle junction has been the subject of earlier studies Janse found that premature right ventricular stimuli failed to retrogradely enter the right bundle but later antegradely activated the right bundle by a pathway utilizing the left bundle He did not however show re-excitation of the right ventricle by this impulse Akhtar and associates[21] found re entry beats in man while measuring right ventricular refractory periods They proposed a re entry pathway within the bundle branches on the basis of the ECG waveform of the re entry beat and delay from right ventricular activation to His bundle activation Left bundle conduction to the proximal right bundle was also found by Janse in experiments where the His bundle was destroyed indicating the His bundle was not a necessary part of the re entry pathway

Castellanos and co workers also noted re entry responses following premature right ventricle stimulation They postulated that these responses were due to local re entry following premature stimulation during the vulnerable period Our study clearly defined a re entrant pathway following right ventricular premature stimulation and demonstrated that the block of conduction in the right bundle branch terminated the occurrence of re-entrant beats

Dissociation of the bundle branches was probably secondary to the longer refractory period of Purkinje-tissue compared to that of the myocardium Slow conduction secondary to the premature response takes place in partially refractory myocardium This serves to allow for the recovery of excitability of the Purkinje-tissue under the left bundle branch and facilitates the retrograde activation of the left bundle branch Re excitation of the right ventricle occurred after intervals as short as only 132/msec Re excitation at this short an interval was made possible by several factors Premature activation itself shortens action potential durations of subsequent excitations as compared to their durations with slower drive Sasyniuk and Mendez[3] reported marked shortening of action potential durations in areas of unidirectional block This shortening was due to electrotonic effects of the unexcited tissue and served to further shorten action potential duration This could suggest that in our re entrant circuit recovery of the previously excited myocardial tissue may be hastened by electrotonic effects from the unexcited right bundle branch and its distal Purkinje system The long delay between arrival of the impulse at the distal right bundle and re excitation of the right ventricle (as shown in Fig 4) may have been due to slow conduction of a local response[36] or may have been due to altered activation of the right ventricle at a site more distant from the recording electrodes

Interruption of conduction in the right bundle branch by either surgical section or by block with anodal currents showed the dependence of right ventricular re entry beats on an intact and functioning specialized conduction system With the production of conduction block in the right bundle premature stimuli that previously caused re entrant beats were unable to do so This finding is strong evidence against the suggestion of Castellanos and colleagues[7] that the re-entry complexes were secondary to local re entry near the premature stimulus The use of anodal conduction block in the in situ heart has not been previously reported Wennemark and associates[3]

however applied anodal currents to isolated portions of the right bundle and found that the areas of hyperpolarization were surrounded by areas of depolarization The conduction across these depolarized areas was due to slow electrotonic conduction The use of anodal blocking currents in vivo could serve as a useful tool for the further investigation of conduction properties of the specialized conduction system

The bundle branch re entry circuit reported in this study differs markedly from other types of in vivo re entry described in the literature It is easily reproducible has fixed pathways of conduction and is of large size These features make it an ideal model for future investigation The key areas within the re entrant circuit can be anatomically localized and thus their electrophysiologic determinates can be quantitated The site of unidirectional block occurs between the right ventricular myocardium and right ventricular Purkinje-muscle junctions It is likely that the disparity of refractoriness between these tissues is the primary factor in forming a site of unidirectional block The slow conduction from the right ventricle to the final common pathway within the proximal left bundle can be easily measured The ability of the site of conduction block at the Purkinje–muscle junction to subsequently conduct antegrade impulses which reactivate the right ventricle can also be quantitated We have shown that shortening of right ventricular recovery facilitated the occurrence of re-entrant beats by enlarging the echo window

It is presumed that the re entrant circuit documented to occur within the specialized conduction system in this report is only one of many that will be demonstrated in the future Since re entry within the specialized conduction system is possible in the normal canine heart it seems likely that bundle branch re entry will occur in man with his larger and often diseased heart These findings suggest yet another mechanism for at least some clinical cases of ventricular tachycardia or flutter

Summary

There is suggestive evidence that bundle branch re entry occurs in man in response to premature right ventricular stimulation Demonstration of the activation sequence during re entrant excitation in the in vivo dog was accomplished by placing recording electrodes on the major portions of the specialized conduction system A temporary right heart bypass was utilized to place two or more electrodes on both right and left bundle branches and place electrodes on the His bundle and on the left and right ventricular endocardium Premature excitation of the right ventricle was found not to retrogradely activate the right bundle but was able to cause slow right to left myocardial activation that resulted in retrograde activation within the left bundle branch Retrograde conduction in the left bundle caused activation of the His bundle and the proximal right bundle Activation of the right bundle resulted in antegrade conduction of the impulse across the site of previous conduction block and re-excitation of the right ventricle to complete the re entrant circuit This type of re entry, utilizing the bundle branches was demonstrated in 19 dogs This re-entry circuit was found to be facilitated by shortening of the right ventricular refractory period by local epicardial warming and was abolished by interruption of conduction in the right bundle by anodal blocking current applied to the right bundle The sites of slow conduction site of unidirectional block and pathways of conduction were demonstrated. The validity of the concept of re entry occurring within the specialized conduction system is substantiated

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Evaluation of the beta blocking drug acebutolol in angina pectoris

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Beta adrenergic blocking drugs are effective in the treatment of angina pectoris the control of hypertension and the management of cardiac arrhythmias Acebutolol hydrochloride (Sectral) is a cardioselective beta adrenergic blocking drug which produces a small decrease in cardiac output has little bronchoconstrictor effect and has not caused ophthalmological or systemic side effects to date

Acebutolol has been used in the management of patients with angina pectoris This study set out to assess objectively the efficacy of acebutolol in the management of angina pectoris in patients with angiographically documented coronary artery disease The study was performed using graded treadmill testing and ambulatory 24 hour ECG monitoring In a third part of the study we compared the value of the two techniques in the assessment of patients with angina pectoris and their response to treatment

Patients

Twenty three patients with typical angina pectoris were included in the study All the patients had undergone cardiac catheterization and coronary angiography and had important coronary artery disease with obstruction(s) of 70 per cent or more in one or more of their coronary arteries The clinical hemodynamic and coronary angiographic findings are given in Table I Three patients who had recurrent important angina pectoris after aortocoronary bypass grafting were included in the study Written informed consent was obtained from each patient before the start of the study

Methods

Protocol The study was divided into four parts patients were studied in the control state at the end of a two week period of treatment with placebo after two weeks treatment with 600 mg acebutolol (200 mg three times per day) and in seven patients after a further two weeks treatment with 1200 mg acebutolol (400 mg three times per day) Patients were examined on each occasion at the same time of day three hours after the morning dose and two hours after a light meal The study was double blind patients did not know whether they were receiving placebo or drug neither did the examining doctor However all the patients had severe angina pectoris and it was felt to be unethical having started treatment with beta blockade to stop the drug suddenly The patients were therefore all treated first with placebo and then unknown to the examining doctor with increasing doses of the beta blocking drug This limits the study in that the effect of physical training on the effort test cannot be evaluated [6] The effect of training is less important however when using 24 hour monitoring to evaluate the patient in his home environment where emotional as well as physical stresses contribute to the development of chest pain

Clinical evaluation of the patient Patients were assessed clinically at each visit and a diary

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Table I. Clinical, hemodynamic, and angiographic data

Patient	Age	Sex	Clinical duration of coronary artery disease (months)	Previous myocardial infarction	Severity of angina pectoris (NYHA grading)	Left ventricular pressure (mm Hg)		Ejection fraction (%)	LV asynergy (%)	Coronary artery obstructions			
						Systolic	End diastolic			LAD system	Circumflex system	RCA	CABG
1	52	male	18	+	3	124	4	30	[illegible]	70	100	100	
2	54	male	9	–	2	200	12	60	–	70	70	–	
3	48	male	8	–	2	170	18	71	–	70	70	60	
4	60	male	108	+	2	165	14	58	40	100	60	100	
5	47	male	24	+	2	160	8	67	30	60	95	60	
6	39	female	27	–	2	180	16	57	20	100	–	100	
7	42	male	18	–	2	116	18	64	–	–	–	70	
8	41	male	72	+	3	130	14	60	20	–	70	100	
9	51	male	60	–	3	160	6	1	–	–	–	100	Small graft
10	48	male	28	+	2	150	10	52	30	–	–	100	
11	53	male	9	–	2	160	12	68	–	90	–	100	
12	53	male	42	+	3	130	14	74	–	90	70	90	
13	45	male	6	–	2	120	16	72	–	–	–	95	
14	59	male	36	+	2	170	17	58	20	90	80	–	
15	62	female	96	+	2	175	28	73	–	90	–	90	
16	47	male	15	–	2	190	16	68	20	80	–	70	
17	56	male	66	+	3	130	18	75	20	80 80	60 90	90 100	
18	45	male	60	–	2	120	10	73	–	100	80	100	
19	70	female	84	–	3	180	16	71	–	–	90	–	
20	4	male	24	–	2	190	14	79	–	–	–	40 60	
21	54	male	192	+	3	130	3	77	30	95 100 90	60 80	100	
22	54	male	18	–	2	160	28	68	–	95	–	–	
23	45	female	6	+	2	130	14	0	20	70	90	100	

was kept of the number of attacks of angina pectoris and the consumption of sublingual nitroglycerin or isosorbide dinitrate. Blood samples were taken for renal and hepatic function tests, the ESR was measured, and tests for antinuclear factor were performed. Ophthalmological and dermatological examination was undertaken at each visit.

Graded treadmill testing. The exercise test was undertaken using the Bruce protocol as modified by the NIH Lipid Research Clinic program, which is standard for our laboratory. A 12 lead electrocardiogram (ECG) was performed at rest. Patients were examined and their heart rate (HR) and blood pressure (BP) were recorded; from these measurements the double product (HR × systolic BP) was calculated. Graded treadmill testing was performed increasing the speed and elevation of the treadmill every 3 minutes (stage 1, 2.7 Kph, 10 per cent elevation; stage 2, 4.0 Kph, 12 per cent elevation; stage 3, 5.5 Kph, 14 per cent elevation; stage 4, 6.8 Kph, 16 per cent elevation; Stage 5, 8 Kph and 18 per cent elevation). The patients were assessed clinically throughout the duration of the test and the ECG was monitored continuously. The ECG was recorded on magnetic tape for later replay and computer analysis and a hard copy was obtained at 1 minute intervals. The HR, BP, and ECG were recorded at the end of each stage of the test; the maximal heart rate achieved during the test was also recorded. The time of onset of ischemic ECG changes (1 mm ST depression 80 msec after the junction) was carefully noted. The test was stopped when the patient developed clinical angina pectoris or when his ST segment depression was severe (> 5 mm depression). In seven patients the test was stopped because of important clinical angina pectoris although the criterion of ischemia (ST depression of 1 mm or more 80 msec after the J point) had not been reached. In all patients the total time on the treadmill was

noted The work performed until the onset of ischemic ECG changes and also until the end of the test was calculated from the formula

Work performed = distance (meters) × % elevation

The heart rate blood pressure and ECG were recorded immediately on cessation of exercise and the double product was again calculated These measurements were repeated at 2 minute intervals until the disappearance of the abnormal ECG changes and of clinical angina pectoris The time of disappearance of abnormal ECG changes and of clinical angina was noted

Ambulatory 24 hour ECG monitoring Continuous dynamic ECG monitoring was undertaken for a 24 hour period at each patient visit Recordings were made on a Holter Avionics dynamic electrocardiograph using a bipolar lead from the right clavicle in the mid clavicular line to the V_5 position The instrument was calibrated so that the monitored lead was matched to Lead V_5 of a standard 12 lead ECG The patients kept a detailed diary of their activities so that the ECG recordings could be examined at comparable levels of physical activity in the control state and during periods of treatment with drug and placebo In order to compare similar activities in the analysis seven exertional levels were developed[11] ranging from the least strenuous (sleeping) to the most severe (heavy exercise) The specific activities included in each exertional level were derived from the diaries of the patients and were given arbitrary numbers related to the relative amount of physical activity performed or emotional stress involved as described by Winsor and Berger Activities included sleeping (1) lying down (2) watching television reading and writing (3) standing dressing and undressing desk work eating a light snack (4) eating a heavy meal housework (5) praying in the synagogue a walk in the cold climbing two flights of steps (6) climbing eight flights of steps (7) The last activity was supervised by a physician For each patient similar activities were considered on each occasion unmatched activities were not included in the analysis

In order to compare the results objectively heart rate and ST segment depression were measured and compared at the same standard exercise load during the control placebo and treatment periods ST segment depression below the isoelectric line was measured 40 and 80 msec after the junctional (J) point of the QRS complex The mean values for ST depression were calculated from five consecutive beats and similarly the mean R R interval was recorded to give the heart rate A detailed profile of dynamic ST segment changes and heart rate changes over 24 hours was therefore obtained for each patient In addition the mean ST depression for the day at 40 and 80 msec and the mean heart rate for the day were calculated from the set of selected activities[11]

Statistical analysis Statistical analysis of the results was performed using Student's paired t test

Results

Clinical response There was a decrease in the number of attacks of angina pectoris ($P < 0.01$) and in the number of sublingual nitrate tablets used ($P < 0.05$) during treatment with placebo five patients said they felt better on placebo Acebutolol (600 mg) produced a marked improvement in the clinical state the number of attacks of angina pectoris halved ($p < 0.001$) as did the consumption of sublingual nitrates ($p < 0.01$) Seventeen patients felt better and six reported no change in their clinical state There was not a statistically significant decrease in the number of attacks of angina pectoris and number of nitroglycerin tablets used on 1,200 mg of the drug Two patients improved further three were unchanged and two felt worse on the larger dose of the drug (Table II)

Graded treadmill testing The results are summarized in Table III There was no change in resting heart rate blood pressure and double product during treatment with placebo Treatment with acebutolol in a dose of 600 mg per day produced a decrease in heart rate ($p < 0.001$) diastolic blood pressure ($p < 0.05$) and double product ($p < 0.05$) there was no further change on the larger dose of acebutolol Treatment with placebo did not increase the time until the onset of chest pain or ischemic ECG changes (ns) but the patients continued for a longer period of time on the treadmill ($p < 0.001$) and performed more work ($p < 0.01$)—this was probably a placebo effect Treatment with acebutolol was associated with improved effort tolerance the time until appearance of chest pain increased ($p < 0.05$) as also the time until appearance of ischemic ECG changes ($p < 0.001$) the total duration on the

Table II Clinical response to acebutolol

	Fortnightly attacks of angina pectoris	Fortnightly consumption of sublingual nitrate	Subjective impression of patient (number of patients)			
			Same	Better	Worse	Comment
Control n = 23	40 ± 29	15 ± 17	–	–	–	–
Placebo n = 23	3? ± 26	13 ± 15	18	5	0	Compared with control
Acebutolol n = 23 (600 mg)	17 ± 16	? ± 8	6	17	0	Compared with control
Acebutolol n = ? (1,200 mg)	5 ± 4	8 ± 10	3	2	2	Compared with 600 mg acebutolol

p < 0.05
p < 0.01
p < 0.001

Table III Graded exercise testing

	Control	Placebo	p	Acebutolol			
				600 mg	p	1,200 mg	p
Resting HR (beats/min)	70 ± 12	68 ± 9	ns	63 ± 8	<0.001	64 ± 6	ns
Resting systolic BP (mm. Hg)	134 ± 17	134 ± 14	ns	127 ± 18	ns	138 ± 22	ns
Resting diastolic BP (mm. Hg)	86 ± 10	85 ± 11	ns	80 ± 11	<0.05	83 ± 14	ns
Resting double product (mm Hg min)	9 406 ± 2 006	9 133 ± 1,833	ns	8,229 ± 1,9?6	<0.05	8,919 ± 2 139	ns
Time until appearance of pain (sec)	136 ± 100	187 ± 139	ns	259 ± 145	<0.05	350 ± 146	<0.05
Time until appearance of ECG changes (sec)	139 ± 71	188 ± 140	ns	366 ± 148	<0.001	247 ± 160	<0.05
Total duration of the test (sec)	210 ± 121	279 ± 146	<0.001	390 ± 167	<0.001	505 ± 134	ns
Total work on treadmill (units)	2 000 ± 1 4?6	3 060 ± 2 408	<0.01	4,983 ± 3 053	<0.001	7,242 ± 3 434	ns
Maximum HR achieved (beats/min)	125 ± 17	1?6 ± 20	ns	108 ± 17	<0.001	119 ± 16	<0.05
Systolic BP (mm HG)	171 ± 23	165 ± 22	ns	154 ± 20	<0.001	152 ± 35	ns
Diastolic BP (mm Hg)	86 ± 16	83 ± 17	ns	?8 ± 11	<0.05	77 ± 15	ns
Double product (mm. Hg min)	?0 686 ± 4,969	20 389 ± 4,861	ns	16,590 ± 4 591	<0.001	15,977 ± 6,527	ns
Time until pain disappears (sec)	116 ± 83	125 ± 105	ns	169 ± 140	ns	130 ± 105	ns
Time until ECG returns to normal (sec)	174 ± 153	184 ± 185	ns	232 ± 243	ns	273 ± 263	ns

Compared with control.
Compared with the lower dose of acebutolol

treadmill ($p < 0.001$) and the total work performed ($p < 0.001$). Administration of a double dose of acebutolol delayed further the onset of chest pain ($p < 0.05$) and the onset of ischemic ECG changes ($p < 0.05$) but the total time on the treadmill did not increase. In two patients receiving the larger dose of acebutolol the test was stopped because of fatigue without the appearance of ischemic ECG changes or the onset of angina pectoris.

The maximum heart rate achieved decreased during treatment with 600 mg acebutolol ($p < 0.001$) and there was a further decrease when the dose was doubled ($p < 0.05$). Systolic and diastolic blood pressure measured immediately after exercise decreased on acebutolol but

Table IV Results of 24 hour monitoring

				Acebutolol			
	Control	*Placebo*	*p*	*600 mg*	*p*	*1200 mg*	*p*
Mean changes during 7 activities							
ST depression (40 msec) (mm)	0.7 ± 0.7	0.7 ± 0.7	ns	0.5 ± 0.5	ns	0.3 ± 0.7	ns
ST depression (80 msec) (mm)	0.7 ± 0.7	0.6 ± 0.8	ns	0.5 ± 0.6	<0.05	0.4 ± 0.8	ns
Heart rate (beats/minute)	94 ± 11	93 ± 10	ns	79 ± 9	<0.001	6 ± 5	<0.01
Changes during maximal activity							
ST depression (40 msec)	1.3 ± 1.2	1.4 ± 1.3	ns	0.7 ± 0.9	<0.001	0.6 ± 1.1	ns
ST depression (80 msec)	1.3 ± 1.7	1.0 ± 1.2	ns	0.7 ± 0.9	<0.05	0.6 ± 1.3	ns
Heart rate (beats/minute)	122 ± 19	124 ± 19	ns	90 ± 15	<0.001	91 ± 15	ns

Compared with control.
Compared with 600 mg acebutolol.

there was no change with the larger dose similarly the double product immediately after exercise decreased with acebutolol 600 mg daily ($p < 0.01$) but there was no further change with the larger dose There was not a significant change in the time until disappearance of chest pain or in the time until return of the ECG to normal

24-hour ECG monitoring There was no change in mean heart rate during the seven selected activities and in heart rate at maximal activity during treatment with placebo nor was there a change in ST depression 40 msec and 80 msec after the J point (Table IV) Treatment with 600 mg acebutolol produced a significant decrease in maximum heart rate ($p < 0.001$) and in ST depression during maximum activity at 40 msec ($p < 0.001$) and 80 msec ($p < 0.05$) When the mean values for the day were considered heart rate decreased markedly ($p < 0.001$) there was a small change at 40 msec (ns) and a significant improvement at 80 msec ($p < 0.05$) Heart rate decreased further with 1 200 mg acebutolol but there was not a further significant change in ST segment depression In general changes in ST segment depression were related to changes in heart rate Improvement in ST segment depression was greatest in patients in whom good beta blocking was achieved and in whom there was a marked decrease in heart rate at rest and during effort In four patients the heart rate observed during maximal activity did not decrease and there was no change in their ST segments during the treatment period

Comparison of graded treadmill testing and 24-hour monitoring In the control state there was a rough correlation between the effort tolerance on treadmill testing and the ST segment changes observed during 24 hour monitoring. The severity of ST depression during 24 hour monitoring we related to the time of onset of ischemic ECG changes during treadmill testing (Fig 1) patients who developed ischemic ECG changes within 100 seconds of the onset of treadmill testing always had more than 1 mm of ST segment depression at 80 msec during their 24 hour monitoring period while patients with less than 1 mm ST segment depression on 24 hour monitoring had a better effort tolerance The range of scatter was greater, however when graded exercise testing was used to assess the patients Both methods produced false negative results four patients who developed ischemic ECG changes on graded exercise testing had no ST depression during 24 hour monitoring while three of the seven patients who did not develop abnormal ECG changes during treadmill testing had 1 mm or more ST depression during 24 hour monitoring and a fourth patient had 0.5 mm ST depression during Holter monitoring The treadmill test had to be stopped in these patients because of fatigue weakness or chest pain before ischemic ECG changes were observed

Comparison between the maximum heart rate observed during 24 hour ECG monitoring and the maximum heart rate achieved during graded treadmill testing is shown in Fig 2 In the control state the maximum heart rate achieved by the two tests was similar in most patients but a greater heart rate was achieved during treadmill testing when the patient received acebutolol

Fig 3 shows the percentage improvement in

maximum ST depression during 24 hour monitoring compared with the percentage increase in total work performed during treadmill testing. Most patients improved their effort tolerance measures by treadmill testing by 50 to 75 per cent but the change in ST depression during 24 hour monitoring was more variable.

Side effects of the drug. There were no changes in measurements of renal and hepatic function nor were there autoimmune or ophthalmological changes in this study.

Discussion

The useful role of beta adrenergic blocking drugs is well established in the treatment of patients with angina pectoris. Beta blocking substances reduce resting myocardial oxygen demand and prevent the unwanted surges in heart rate and blood pressure which occur during effort or emotional excitement to upset the myocardial oxygen supply–demand balance in patients with coronary artery disease. The frequency of attacks of clinical angina pectoris is reduced and possibly also the number of episodes of myocardial infarction; longevity may be increased.[11]

The present study shows that the beta blocking drug acebutolol is an effective antianginal agent; angina pectoris is ameliorated, effort tolerance is improved, and the amount of ischemic ST segment depression on the electrocardiogram is decreased. A good response was achieved on 600 mg of the drug. On the larger dose the time until ischemia during treadmill testing was increased as measured both by the onset of anginal chest pain and by the onset of appearance of ischemic changes on the electrocardiogram. However, although the total duration of the test increased, the increase was not statistically significant since some patients stopped exercising because of fatigue and weakness, presumably a result of an inadequate cardiac output. It is also interesting that the larger dose of acebutolol did not decrease further the mean ST segment depression during 24 hours free ranging activity in the home environment. This may be due to the fact that ST depression 8 msec after the J point was already less than 0.7 mm on the smaller dose of the drug. We did not measure blood levels of acebutolol and have no information relating to the blood levels achieved on the two constant oral doses of the drug.

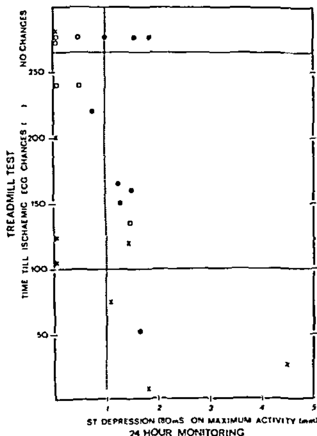


Fig 1. Comparison between ST segment depression (mm) (80 msec after the J point) during maximal free-ranging activity recorded by 24 hour monitoring and time till appearance of ischemic ECG changes on graded treadmill testing. Patients who developed ischemic ECG changes within 100 seconds of the onset of treadmill testing always had more than 1 minute ST depression during 24-hour monitoring. *The upper panel* refers to seven patients who had no ischemic ECG changes during treadmill testing; four of them had 0.5 mm or more ST depression during 24 hour monitoring. (o = patients with single vessel coronary disease; ● = double vessel disease; X = triple vessel disease.)

Both graded treadmill testing and 24 hour monitoring were diagnostic of ischemic heart disease in most patients but both methods produced false negative results. For quantitating effort tolerance, treadmill testing is far superior to 24 hour monitoring since the test is reproducible and objective, but patients must cooperate during treadmill testing and a false negative result may be obtained if the patient refuses to continue the test or is limited by physical weakness or deformity so that he does not increase his heart rate and cardiac output to the point of ischemia. In our study four such patients showed diagnostic ST segment depression during 24 hour

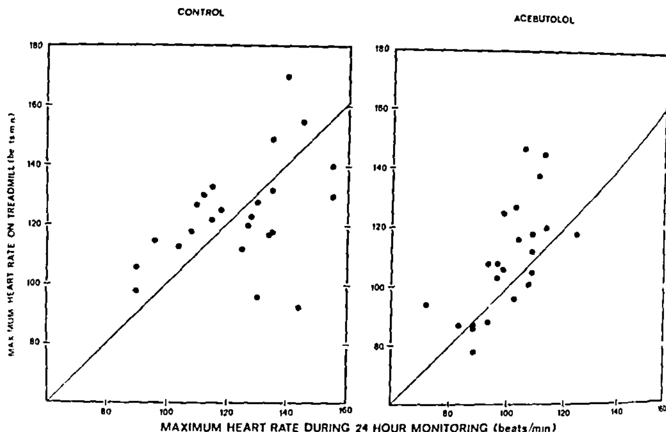


Fig 2 Maximum heart rate during 24 hour monitoring and during treadmill testing in the control state *(left hand graph)* and on 600 mg acebutolol *(right hand graph)* When receiving acebutolol, patients reached a lower heart rate in their own home environment than the rate to which they could be taken during treadmill testing

monitoring Twenty four hour monitoring is ideally suited for studying the patient in his daily environment where ischemia is induced by emotional as well as by physical factors but 24 hour monitoring fails to show ischemic ST changes if the patient curtails his activity during the period of study In treadmill testing a greater heart rate is achieved in most patients myocardial oxygen requirement is greater and this increases the chances that a positive diagnosis will be made

In some patients tachycardia was observed on 24 hour monitoring during emotional stress or excitement (such as praying in the synagogue) and this was accompanied by severe ST segment depression In these patients great benefit was obtained from beta blockade since acebutolol effectively controlled emotionally induced tachycardia In contrast physical exertion of necessity requires a given increase in heart rate and cardiac output to provide adequate oxygen delivery to the tissues For this reason Holter monitoring often showed a smaller improvement in heart rate and ischemic ST depression during physical exercise than during emotional excitement in the treatment period

In summary acebutolol is an effective antianginal drug both as assessed by graded exercise testing and by 24 hour ambulatory ECG monitoring The methods are complimentary in evaluating patients with ischemic heart disease and the response to therapy—graded exercise testing for quantitating effort tolerance and the improvement with therapy and Holter monitoring for assessing the progress of the patient in his daily environment

Summary

The effects of the beta adernergic blocking drug acebutolol were studied in 23 patients with angina pectoris and angiographically documented coronary artery disease Patients were evaluated clinically by graded treadmill testing and by 24 hour Holter monitoring in the control state after 2 weeks treatment with placebo and after 2 weeks treatment with 600 mg and then 1 200 mg.

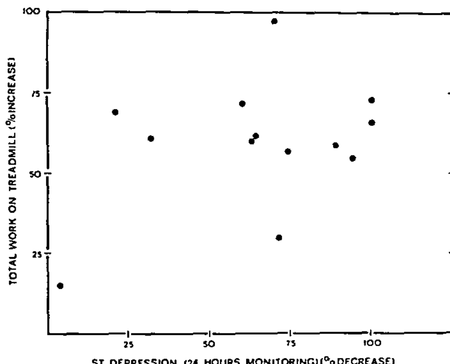


Fig 3 Improvement in ST segment depression recorded by 24 hour monitoring compared with improvement in effort tolerance during treadmill testing in patients receiving 600 mg. acebutolol. Most patients improved their treadmill effort tolerance by 50 to 75 percent but the improvement in ST depression on 24 hour monitoring was variable (Patients with < 0.5 mm ST depression on their initial 24-hour monitoring study not included in this graph).

of acebutolol Acebutolol (in a daily dose of 600 mg) was an effective antianginal drug the number of clinical attacks of angina pectoris ($p < 0.001$) and the consumption of sublingual nitrate decreased ($p < 0.01$) there was a significant increase in the treadmill effort tolerance as measured by the time to appearance of ischemic ECG changes ($p < 0.001$) and the total work performed ($p < 0.001$) and there was also a significant decrease in ischemic ST segment depression on 24 hour Holter monitoring Treatment with 1,200 mg acebutolol was associated with a further decrease in heart rate and a further improvement in effort tolerance on treadmill testing ($p < 0.05$) On the large dose of the drug however there was no further clinical improvement and no further improvement on 24 hour ECG monitoring several patients complained of weakness and fatigue

Graded treadmill testing was an excellent objective method for assessing physical effort tolerance and its improvement after treatment with the beta blocking drug Twenty four hour Holter monitoring was a useful and complementary test especially in patients who stopped exercising on the treadmill because of fatigue or weakness and especially for assessing the efficacy of beta blockade in controlling emotionally induced tachyacrdia and ischemia in the patient s own daily environment

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Low output syndrome in right ventricular infarction

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Myocardial infarction has always been considered as a left ventricular disease However it has been possible to observe the existence in necropsy studies of right ventricular involvement as an infrequent anatomical finding

During the last few years the interest in right ventricular infarction is increasing Some reports have been published about its echocardiographic scintigraphic electrocardiographic and hemodynamic characteristics

We describe in this report a number of patients with right ventricular infarction and low output syndrome in whom hemodynamic monitoring was performed We studied the function of both ventricles and from these studies we will make recommendations about the differential diagnosis treatment and prognosis of these patients

Materials and methods

Between November 1977 and April 1978 140 patients with acute myocardial infarction were admitted into our Coronary Care Unit In 120 of them hemodynamic monitoring was performed For a variety of reasons hemodynamic studies were not made in the rest of the patients but none of them showed clinical heart failure or low output All of the patients were admitted within the first 24 hours of evolution

We selected ten patients with low ouput syndrome and right atrial pressure disproportionately increased in relation to left ventricular filling pressure for this reason the diagnosis of right ventricular infarction was made Nine of these patients were men and one was a woman their ages ranged from 42 to 82 years (average 65 years)

Right heart catheterization was performed at admission by inserting a Swan Ganz thermodilution catheter into the pulmonary trunk through the right antecubital vein Right atrial right ventricular pulmonary artery and pulmonary capillary wedge pressures were recorded through a Hewlett Packard 1280 transducer in a Siemens Elema Mingograph 34 at a paper speed of 25 mm per second Right ventricular pressure was measured at withdrawal when it was possible

Cardiac output was determined by thermodilution using an Edwards 9500 computer In every case at least three succesive determinations were made calculating the average vlaue

Arterial blood pressure was measured by arm cuff in mm Hg In some patients it was also measured by intra arterial catheter

Hemodynamic parameters were calculated according to the formulas proposed by Yang and colleagues and by Russell and Rackley[13] As have these authors we calculated the stroke net and diastolic work index as three different entities $LVSWI = SI \times \overline{ASP} \times 0.0136$ where LVSWI is left ventricular stroke work index in gm /beat/M $\overline{ASP}$ is mean aortic systolic pressure in mm Hg and 0.0136 is the conversion factor from mm Hg ml to gm $\overline{ASP} = 0.8$ (aortic systolic − aortic diastolic) + aortic diastolic pressure $LVNWI = SI \quad (\overline{ASP} - \overline{PCP}) \times 0.0136$ where LVNWI is left ventricular net work index and $\overline{PCP}$ is mean pulmonary capillary pressure in

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Table I Clinical data in 10 patients with right ventricular infarction and low output syndrome

Case no	Obstructive lung disease	Previous hypertension	FCC	Chest x ray	Complete heart block	Pacemaker	Atrial arrhythmias	Mortality
1	+		IMI	Lungs clear	+	+		
2			IMI	Lungs clear	+			
3			IPMI	Lungs clear	+	+	Paroxysmal fibrillation	
4			IMI	Lungs clear	+	+		+
5			IPMI	Pulmonary congestion	+	+	AV junctional rhythm	
6		+	IMI	Lungs clear			AV junctional rhythm	
7	+		IPMI	Lungs clear	+			+ Autopsy
8			LBBB		+		PAC SA block	+ Autopsy
9	+	+	IPMI	Pulmonary congestion Cardiomegaly	+	+	Atrial fibrillation AV junctional rhythm	
10		+	IPMI	Pulmonary congestion	+	+	Sinus arrest paroxysmal tachycardia	+ Autopsy

AV = atrioventricular; IMI = inferior myocardial infarction IPMI = inferoposterior myocardial infarction LBBB = left bundle branch block PAC = premature atrial contractions SA = sinoatrial.

mm Hg LVDWI = LVSWI − LVNWI where LVDWI is left ventricular diastolic work index

Right ventricular work indexes were calculated using similar formulas with $\overline{PSTP}$ (mean pulmonary systolic trunk pressure) instead of $\overline{ASP}$ and $\overline{RAP}$ (mean right atrial pressure) instead of $\overline{PCP}$

For the purposes of this study the low output syndrome was defined as a cardiac index below 2 2 liters/min per square meter [14] with evidences of reduced tissue perfusion such as mental impairment and oliguria or anuria Some of our patients were in shock [15] but others did not show signs of peripheral vasoconstriction For this reason we prefer to talk about low output syndrome rather than shock

Results

Clinical manifestations (Table I) Three patients had a previous history of high blood pressure and three had suffered chronic obstructive lung disease

Every patient had severe low output syndrome Jugular venous pressure was always increased with or without hepatomegaly Chest x ray films were normal except in three who showed pulmonary congestion

Electrocardiogram (Table I) In four patients the myocardial infarction was inferior in another five it was inferoposterior and in one a bundle branch block pattern made it impossible to locate the necrosis All but one showed complete atrioventricular block and in six of them temporary transvenous pacing was necessary Eight patients presented supraventricular arrhythmias such as sinus arrest sinoatrial block premature atrial contractions or atrial fibrillation at some point. In any case these arrhythmias were permanent, and all patients recovered the sinus rhythm with normal atrioventricular conduction within one to ten days

Hemodynamics At admission the common hemodynamic features were the following

High mean right atrial pressure (average 16 3 ± 5 2 mm Hg) with similar values for the mean pulmonary capillary pressure (average 15 ± 4 5 mm Hg) (NS)

The right atrial pressure pulse exhibited a restrictive pattern with a deep y descent

Mean pulmonary capillary pressure was normal In only two patients was it higher than 18 mm Hg (Nos 21 and 22 respectively) In every case it was similar to the pulmonary diastolic pressure

Cardiac index was less than 2 liters/min M The average value was 1 42 ± 0 45

Right ventricular diastolic work index was very high (6 26 ± 3 63 gm /beat/M) being in most patients higher than the net work index (3 28 ± 1 86)

In the left ventricle the diastolic work index was 5 75 ± 3 15 gm /beat/M and the net work index was 21 25 ± 8 48

The ratio net/stroke work index of the right

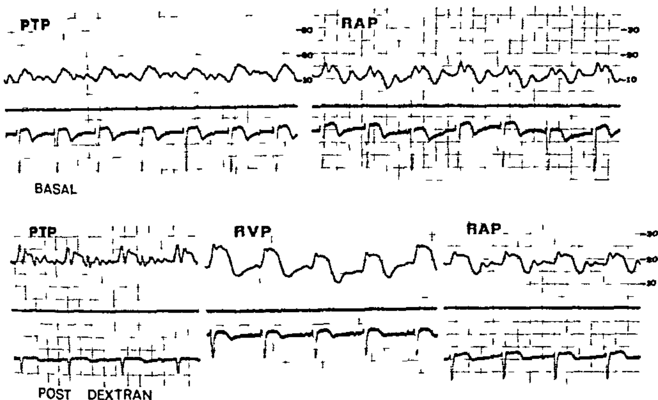


Fig 1 Case 1 Pulmonary trunk (*PTP*) and right atrial (*RAP*) pressures (mm Hg) are shown in basal conditions and after volume expansion (we have also registered right ventricular pressure [*RVP*]) Note the similarity between these pressures

ventricle (average 0 33 ± 0 13) was always inferior to the same ratio in the left ventricle (0 79 ± 0 08)

Right and left ventricular function curves were constructed in every patient with volume expansion comparing net and diastolic work index with filling pressure (Fig 5) The net work index curve was always flat or depressed in the right ventricle whereas in the left ventricle it was ascending flat or depressed The diastolic work index curve was very high in the right ventricle and normal in the left ventricle

Individual findings The right atrial pulse was very similar to the right ventricular and pulmonary trunk pressure pulse in patients No 1 and 4 In the rest of the patients the systolic pulmonary pressure was superior to the right atrial pressure Examples of both types of pressures are shown in Figs 1 and 2

Clinical management While some patients needed a great deal of fluid in quick intravenous infusion in other cases it was necessary to employ slow infusion of fluids and vasodilators because the pulmonary capillary and right atrial pressures rose too much At other times we could not observe any improvement after a fluid tolerance test and all these patients were treated with dopamine Their clinical and hemodynamic condition slowly improved and in four to nine days the drugs could be discontinued

Evolution and mortality Two patients (Cases No 4 and 8) died in the two first hours after admission Patients No 7 and 10 died suddenly on the seventh and eleventh day of evolution respectively when they had been allowed to get up after having recovered from the low output syndrome The six survivors continued in good health and without any signs of cardiac insufficiency after a follow up of five to nine months

Autopsy findings Postmortem studies were made in three of the four dead patients each of these cases had severe diffuse coronary artery disease with acute necrosis in both the left ventricle and the right ventricle Two cases (No 7 and 8) were complicated by pulmonary emboli in patient No 7 the emboli was the cause of the

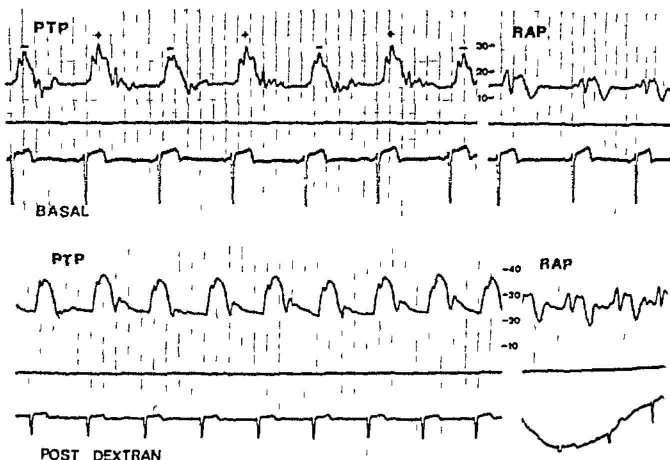


Fig 2 Case 6 Pulmonary trunk (*PTP*) and right atrial (*RAP*) pressures (mm Hg) before and after volume overload Note the pulmonary pulsus alternanas and the systolic pulmonary pressure higher than right atrial pressure this is similar to diastolic pulmonary trunk pressure and shows a prominent y descent

sudden death and in patient No 8 it was nonocclusive Case No 10 showed a rupture of the free wall of the left ventricle Right ventricular hypertrophy and dilatation were found in patients No 7 and 10

Discussion

The disproportionate increase of the right atrial pressure in relation to left ventricular filling pressure in acute myocardial infarction is a characteristic finding of right ventricular infarction Only in 12 of our 120 patients (10%) with acute myocardial infarction and hemodynamic monitoring did right atrial pressure reach the values of the left ventricular filling pressure Ten of these cases exhibited the characteristics of low output syndrome and are the patients we study here Therefore we can say that low output syndrome is a very frequent condition in right ventricular infarction

Right atrial pressure may also be increased in cases of chronic obstructive lung disease or pulmonary thromboembolism but in such situations the pulmonary capillary pressure is lower than the diastolic pulmonary trunk pressure The hemodynamic findings in constrictive pericarditis and cardiac tamponade may be similar In Fig 3 the pulmonary right ventricular and right atrial pressure of a patient with acute myocardial infarction and chronic constrictive pericarditis are shown The right atrial pressure tracing is similar to the one observed in cases of right ventricular infarction (Fig 2) The right ventricular protodiastolic dip in the patient with constrictive pericarditis reached zero mm Hg In our patients with right ventricular infarction the dip failed to reach zero values However these differences are of no significance because similar tracings may be observed in both conditions so we think that the previous history is of great value to establish differential diagnosis

When cardiac tamponade occurs during acute

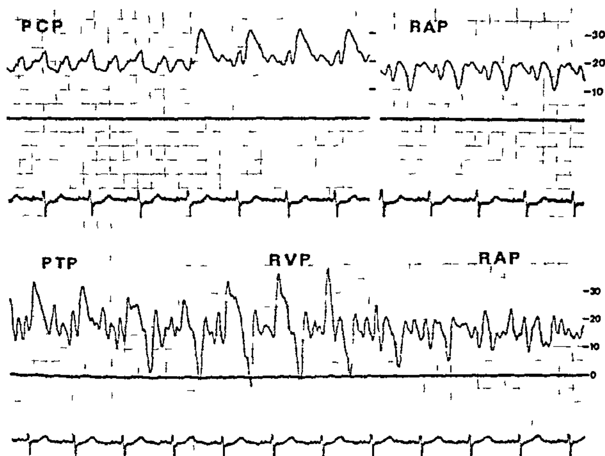


Fig 3 Pulmonary capillary (*PCP*) pulmonary trunk (*PTP*) right ventricular (*RVP*) and right atrial (*RAP*) pressures (mm Hg) in a patient with acute myocardial infarction and chronic constrictive pericarditis Note the prominent "y" descent in right atrial pulse and the protodiastolic dip in right ventricular pressure tracings Right atrial pressure reaches the pulmonary capillary values

myocardial infarction right atrial pressure increases and pulmonary trunk pressure decreases Fig 4 shows right atrial and pulmonary pressures in a patient with acute myocardial infarction before and during cardiac tamponade due to proved cardiac rupture Note that right atrial pressure reached diastolic pulmonary pressure values but failed to show the deep y descent characteristic of right ventricular infarction Echocardiography may also be of value to establish diagnosis

Clinical features These patients show very clearly defined clinical characteristics which make it possible to suspect the diagnosis of right ventricular infarction before hemodynamic data are obtained They are patients with acute posterior or inferior infarction with high enzymatic values Central venous pressure is very high and there are no signs of pulmonary congestion Atrioventricular block or supraventricular arrhythmias are very frequent (Table I) and make the clinical situation of low output worse Three of our patients (30%) had chronic obstructive lung disease this is in accordance with Wade s theory [3] about a high incidence of infarction in previously hypertrophic right ventricles

Hemodynamics All our patients had a very low cardiac index and most of them were included in subset III of Forrester and associates[1] only two had a pulmonary capillary pressure above 18 mm Hg and were in subset IV

The most characteristic finding of these patients is that the right atrial pressure is equal in magnitude to the pulmonary capillary pressure in two of them the right atrial right ventricular and pulmonary trunk pressure tracings were very similar Probably these patients have the greatest damage of the right ventricle and right

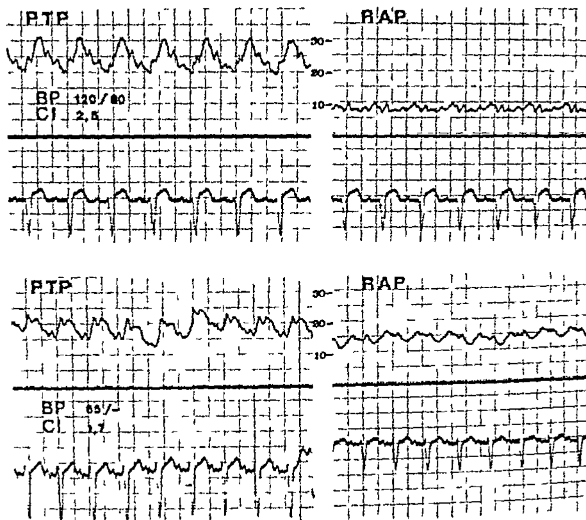


Fig 4 Pressure tracings in mm Hg before and during cardiac tamponade Right atrial pressure (RAP) is similar to diastolic pulmonary trunk pressure (PTP) but fail to show the deep y descent BP = blood pressure in mm Hg CI = cardiac index in liters/min/M

pressure is passively transmitted to the pulmonary trunk Another common feature is the right atrial pulse tracing in every case it showed a more or less prominent y descent as in constrictive pericarditis (Figs 1 2 and 3) Probably an impairment in diastolic function is always present in right ventricular infarction

Ventricular function curves were constructed after volume expansion comparing filling pressure with net and diastolic work index for each ventricle In accordance with other authors right ventricular net work index curves were flat or depressed However right ventricular diastolic work index the work spent in expanding the right ventricle always increased and these values were superior to the net work index (Fig 5) On the other hand left ventricular net work index curves were ascending flat or depressed but always showed superior values to the diastolic wor index This proves that right ventricular functio is always severely impaired and left ventricul function is variable

Treatment Quick administration of fluids h been proposed as the treatment of choice in ri ventricular infarction if pulmonary capilla pressure is high vasodilators are indicated both situations the purpose is to establish pressure gradient between the right and left atr to improve the pulmonary circulation when th right ventricle is ineffective

In our patients the amount of fluid admini tered varied greatly for the increase of right atri pressure It may be due to differences in ri ventricular compliance and volume depletion each patient We have observed that with simil pressure values the clinical condition was ve

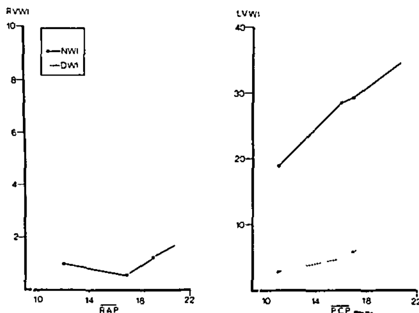


Fig 5 Case 1 Right (RV) and left (LV) ventricular function curves. Note that the net work index curve (NWI) is flat in RV and ascending in LV Diastolic work index (DWI) has very high values in the RV superior to the NWI values. Work index is measured in gm /beat/M $\overline{RAP}$ = mean right atrial pressure and $\overline{PCP}$ = mean pulmonary capillary pressure

different in every patient It may be explained by the different participation of the left ventricle The poorer response to fluid administration was observed in the patients with worse left ventricular function on the other hand patients with severe low output but a good left ventricular function improved in a brief period of time We obtained good response in some patients with dopamine administration and we think it is indicated when they fail to improve with volume expansion and are too hypotensive to use vasodilating drugs

Anticoagulants must probably be used in all patients with right ventricular infarction because of their high risk of thromboembolic complications [*] proved in the autopsy studies of our patients

Prognosis The mortality rate in our cases of right ventricular infarction with severe low output was very high 40% However in two of them (20%) the death was not due to low output but to other causes such as pulmonary embolism and rupture of the left ventricle In three patients postmortem studies were performed and both ventricles had severe damage This supports the possibility that coexisting left ventricular damage may account in part for the bad prognosis of these patients poor left ventricular function has bad prognosis itself and the correct treatment of the low output syndrome (fluid administration) is more difficult in these cases

The massive destruction of the right ventricle demonstrated by the failure to generate pulmonary pressures is follow by severe hemodynamic changes especially low output or shock However the prognosis of these patients is not necessarily bad if the diagnosis is made soon and the proper treatment is established

For the correct treatment of these patients hemodynamic monitoring is mandatory because there are important individual differences depending especially on right ventricular compliance and left ventricular dysfunction

Summary

In this paper we describe clinical and hemodynamic data in ten patients with right ventricular infarction and low output syndrome Atrioventricular block and supraventricular arrhythmias were a common finding All of them had a right atrial pressure disproportionately increased (average 16 3 ± 5 2 mm Hg) in relation to left ventricular filling pressure (average 15 ± 4 5 mm Hg) and a very low cardiac index (average 1 42 ± 0 45 liters/min /m) The right atrial pulse tracings were similar to those of constrictive pericarditis showing a deep y descent in every patient We made the differential diagnosis

between similar hemodynamic entities and constructed function curves of right and left ventricles Right ventricular diastolic work index was always increased (average 6 26 ± 3 63 gm /beat/M) being higher than net work index (average 3 28 ± 1 87 gm /beat/M) While all function curves of the right ventricle were flat or depressed those of the left ventricle were very different Treatment consisted mainly of fluid overload and in some cases of vasodilators or dopamine Mortality rate was 40% We think that coexisting left ventricular damage may account in part for the bad prognosis of these patients

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Ethmozin: A new antiarrhythmic agent developed in the USSR. Efficacy and tolerance

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In 1964 ethmozin, the ethyl ester hydrochloride of 10(3-morpholinopropionyl) phenothiazine-2-carbamic acid (Fig. 1), was synthesized by A. N. Gritsenko, Z. I. Yermakova, and S. V. Zhuravlev at the Institute for Pharmacology of the Academy of Medical Sciences of the USSR. Other phenothiazines have been reported to possess antiarrhythmic properties, and early clinical and experimental trials with ethmozin have shown it to be a potentially effective and safe agent for the control of atrial and ventricular arrhythmias in a variety of clinical settings. However, well-controlled protocols using long-term ambulatory electrocardiographic monitoring have not been employed. Electrophysiologic studies have not yet been conducted in man. In isolated non-ischemic canine Purkinje fibers ethmozin demonstrated electrophysiologic characteristics similar to lidocaine. Ethmozin produced a dose-dependent decrease of both maximum upstroke velocity of phase 0 depolarization and action potential duration. Unlike lidocaine, ethmozin did not effect the slope of phase 4 depolarization of spontaneous automatic Purkinje fibers. However, in ischemic Purkinje fibers ethmozin did decrease the slope of phase 4 depolarization (Dr. Brian Hoffman, personal communication). In studies of experimental myocardial infarction in conscious dogs, ethmozin was effective in suppressing arrhythmias that occurred 24 hours or longer after occlusion and was more effective than quinidine given in comparable doses. This report details the first clinical experience with short-term administration of ethmozin in the United States using a single-blinded placebo-controlled protocol and extensive ambulatory electrocardiographic monitoring to evaluate drug efficacy, tolerance, and pharmacokinetics.

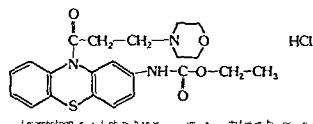


Fig. 1. Chemical formula and name for ethmozin.

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Methods

Patient population. Patients were referred for study from the cardiac practices of physicians at the Hospital of the University of Pennsylvania and the Philadelphia Veterans Administration Hospital after informed consent was obtained. Patients were clinically stable and none had evidence of acute myocardial infarction within 3 months of study, or had concurrent active illnesses, second or third degree atrioventricular block, sick sinus syndrome, electrolyte or acid-base disturbance, or were on chemotherapeutic

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Table I Clinical data in study population including the initial 3 day control frequency of ventricular premature depolarizations (VPDs) and atrial premature depolarizations (APDs)

Patients				Daily dose of ethmo in		Mean hourly ectopic frequency during 3 control days	
No	Age	Sex	Cardiac diagnosis	mg	mg/kg	VPDs	APDs
1	31	M	VHD	225	2.4	–	207
2	52	M	CCM	225	3.0	143	121
3	67	M	ASH	225	3.0	–	63
4	60	M	HCVD	300	3.3	360	–
5	65	M	CAD	300	4.6	48	117
6	57	M	VHD	450	5.8	539	–
7	44	M	HCVD	300	3.3	1433	–
A				450	4.7	13 9	–
B				600	6.4	1306	–
8	68	F	CAD	300	4.0	218	–
A				450	5.8	414	–
9	34	M	CAD	450	6.6	1801	–
A				600	9.0	685	–
10	61	M	CAD	450	5.8	18	–
11	63	M	None	450	4.8	–	693
12	64	M	None	600	10.0	115	287
A				750	11.2	–	89
13	48	M	None	600	5.0	65	–
14	[illegible]	M	CAD	600	6.3	231	–
15	65	M	HCVD	600	8.2	516	98
16	64	M	CAD	600	8.8	88	–
17	60	M	CAD	600	7.4	58	359

M = male F = female VHD = valvular heart disease CCM = congestive cardiomyopathy ASH = asymmetric septal hypertrophy HCVD = hypertensive cardiovascular disease CAD = coronary artery disease

agents All 17 patients had non life threatening ventricular and/or atrial arrhythmias The arrhythmias were considered 'non life threatening if they did not cause hemodynamic consequences or electrical instability such that short term placebo therapy was associated with no measurable risk to cardiovascular stability Patients with paroxysmal ventricular tachycardia were accepted if they met these criteria and if the episodes lasted less than 1 minute before spontaneous conversion to normal sinus rhythm

The patients included 16 men and one woman with a mean age of 56 ± 12 (SD) years (range 31 to 68 years) (Table I) Three patients underwent two and one patient had three dosing periods from 8 to 12 weeks apart providing 22 dosing periods for analysis Fourteen patients had ventricular premature depolarizations (VPDs) on the average ranging from 48 to 1,801 depolarizations per hour during the 3 day control period and provided 18 dosing periods for analysis Eight patients had atrial premature depolarizations (APDs) on the average ranging from 63 to 693 depolarizations per hour during the 3 control days and provided nine dosing periods for analysis Seven patients had coronary artery disease three had hypertensive heart disease two had valvular heart disease (one had a mitral prosthesis for mitral prolapse and the other an aortic prosthesis for infective endocarditis on a bicuspid aortic valve) one presented with congestive cardiomyopathy, one had asymptomatic asymmetric septal hypertrophy and three had no clinical evidence of heart disease Nine of the 14 patients with VPDs and three of the eight patients with APDs had been previously treated unsuccessfully with antiarrhythmic agents

Protocol A single blind placebo controlled protocol was employed in which all patients were hospitalized in the clinical research center for 14 days In patients No 1 to 3 ethmozin was given according to the following schedule day 1 no medicine days 2 to 4 placebo days 5 to 7 ethmozin 150 mg/day days 8 and 9 ethmozin 225 mg/day days 10 and 11 ethmozin 300 mg/day and days 12 to 14 placebo Drugs were administered in patients No 4 to 17 in the following manner day 1 no medicine days 2 to 4 placebo days 5 to 11 ethmozin at doses listed in Table I days 12 to 14 placebo Both placebo and ethmozin tablets were identical in appearance and each was given every 8 hours Ethmozin dose in these patients varied from 300 to 750 mg/day (2.4 to 11.2 mg/kg/day)

Patients were monitored in the clinical research center to insure that their daily activities would remain as close to uniform as possible to minimize the influence of changes in activity on ectopic frequency Furthermore the prior medical regimens were held constant in each patient and no change in their clinical status was observed during the 14 days of hospitalization All prior antiarrhythmic agents were discontinued at least 5 days before study During the entire 13 days of placebo-ethmozin dosing patients underwent 24 hour long term electrocardiographic monitoring (Holter Monitoring) using a 445 Avionics two channel (V_1 and V_5 electrodes) recorder Careful attention was given to skin care and the electrode

Table II Effect of ethmozin on atrial premature depolarizations (APDs) individual patient results

Patient No	Control mean APDs per hour	% change from control during ethmozin			
		Mean change		Maximum decrease	
		Arithmetic	Logarithmic	Arithmetic	Logarithmic
1	907	−56	−49	−76	−82
2	121	−64	−61	−100	−100
3	63	−60	−39	−87	−74
5	117	−85	−92	−100	−100
11	693	−3	−9	−33	−45
12	89	+46	−32	−93	−95
15	98	−67	−25	−94	−88
17	359	−71	−98	−100	−100

(p < 0 05)

Wilcoxon sign rank test for statistical significance ( ) was employed only for the mean logarithmic changed data In all other columns, a change of >60% should be used to consider reductions statistically significant See text for detail.

site was changed daily Routine 12 lead electrocardiograms were taken on the day of admission on the second placebo day and on the fourth and seventh day of ethmozin use The following were obtained after a 12 hour fast on the day of admission the first placebo day the fourth day of ethmozin dosing and on the first day of the post ethmozin placebo period routine urinalysis complete blood counts (including platelet counts and white cell differential) aspartate amino transferase alanine aminotransferase alkaline phosphatase bilirubin calcium lactic acid dehydrogenase urea nitrogen glucose phosphorous creatinine uric acid total protein albumin cholesterol triglycerides sodium potassium chlorides and carbon dioxide

Blood for ethmozin plasma levels were taken during the placebo period and then at 1 2 5 8 24 25 49 73 97 121 145 169 and 193 hours after initiation of ethmozin dosing Twenty four hour urine and stool collections were obtained before and during each day of ethmozin dosing to determine ethmozin excretion patterns Vital signs and daily body weights were recorded in relation to ethmozin dosing periods

Ethmozin concentration in plasma urine and feces was determined by C C Whitney Jr Ph D (du Pont Company Newark Delaware) Ethmozin was analyzed using a liquid chromotographic method that detects only unaltered ethmozin

Ethmozin elimination half life was also determined in five healthy adult male volunteers (age range 24 to 32 years) after a single 500 mg oral dose of ethmozin with plasma level determinations at 1/4 1/2 3/4 1 1 1/4 1 1/2 1 3/4 2 3 4 6 8 10 12 16 24 30 36 42 and 48 hours

Data analysis All long term electrocardiographic tapes were analyzed by an independent research service* without knowledge of the type of medication used during the recording The tapes were processed using an Avionics 660A scanner with the same group of trained analysts Accuracy of ectopic frequency using this system was determined by the use of real time analyzed tapes with average VPD frequency varying from 0 to over 1 000 per hour The mean relative error rate was 7 0 per cent In this study ventricular couplets multiform complexes and ventricular tachycardia were not specifically quantified

Statistical analysis The effect of ethmozin on VPD and APD frequency was analyzed using both linear and logarithmic methods Transformation to natural logarithms was used to insure that the assumption of normal distribution and homogeneous variance would be more closely satisfied for statistical analysis Since zero arrhythmic frequency was present in some hours each hourly arrhythmic frequency was increased by one before the logarithm was computed The mean frequency of arrhythmia data obtained during the initial 72 hour placebo periods (control) was used to compute the control frequency The control period was tested against ethmozin considering three periods of treatment all 7 days the last 5 days and the last 2 days of ethmozin therapy Results were similar regardless of the treatment period chosen therefore only the data using all 7 days is reported The Percentage mean change using either arithmetic or logarithmic data was defined as [(100) × (the mean

*Anthropometrics Inc Haddonfield N J

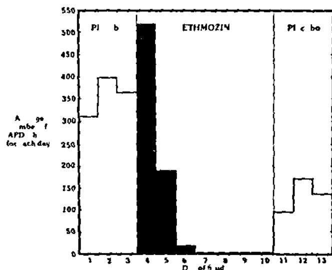


Fig 2 The frequency of atrial premature depolarizations (APD) are depicted during placebo during ethmozin at 600 mg per day and during a post placebo period in patient No 1

arithmetic frequency per hour during the 3 control days minus the mean arithmetic frequency per hour for all 7 days of ethmozin dosing)] + [the mean arithmetic frequency per hour during the 3 control days] In addition a percentage maximal change using either arithmetic or logarithmic data was calculated using the same formula except that instead of all 7 days of data on ethmozin being used only the day of maximum reduction in arrhythmia frequency during ethmozin dosing was used Sixty per cent reduction from control during ethmizon dosing was chosen as the level at which significant change ($p < 0.05$) was reached based on a four factor nested analysis of variance of the arrhythmia frequency during the control periods The analysis revealed such a great degree of spontaneous variability in VPD frequency that a 58 per cent reduction level during ethmozin dosing was required to define a change that was not likely due to spontaneous variability alone even though we employed continuous monitoring for 13 days and had three control and seven test periods

The mean logarithmic change was also subjected to a one sample Student s t test and the Wilcoxon sign rank test for paired differences to determine whether ethmozin had any significant ($p < 0.05$) effect on arrhythmia frequency when compared to the control period

Results

Efficacy *Atrial premature depolarizations* The mean hourly rate of APDs during ethmozin therapy was reduced by >60 per cent of control frequency in five of eight (63 per cent) patients when analyzed by the linear method significant reductions in APDs were noted in 6 (75 per cent) of eight patients when the logarithmic method was used Using either method the maximal hourly frequency of APDs was reduced by >70 per cent from control levels in seven of eight patients (88 per cent) The individual patient data are depicted in Table II in those patients dosed more than once the data pertain to the maximal dose employed An illustrative patient example showing raw APD frequency is depicted in Fig 2 while mean APD frequency data during each protocol period are depicted in Fig 3

Ventricular premature depolarizations Using arithmetic change analysis on all patients irrespective of ethmozin dose employed seven of 14 patients had a greater than 60 per cent reduction in the mean hourly VPD frequency as compared to the placebo period Using logarithmic change analysis 10 of 14 patients (71 per cent) had a significant reduction in the mean VPD frequency Using either arithmetic or logarithmic analysis 10 of 14 patients (71 per cent) had a greater than 60 per cent reduction in the maximal hourly VPD frequency compared to control Individual patient data are depicted in Table III using the maximal dose employed in those patients dosed more than once An illustrative patient example in which two different dosing regimens were used separated by an 8 week rest period is depicted in Fig 4 and suggests that the degree of VPD frequency reduction may be related to the dose of ethmozin The mean VPD frequency data during each protocol period as related to the dose of ethmozin received are depicted in Fig 5

Tolerance When the periods of ethmozin and placebo treatment were compared no differences appeared in blood pressure mean heart rate oral body temperature body weight P R QRS or QT interval the morphology of the beats or laboratory values tested The only symptom reported during ethmozin treatment was mild nausea in one case (Patient No 1)

Pharmacokinetics Intact ethmozin was found in small amounts (<1 per cent) in feces and urine suggesting that it undergoes extensive and rapid metabolism after absorption Ethmozin dose in mg /Kg showed significant relationships with the area under the plasma ethmozin curve (r = 0.5 $p < 0.01$) peak plasma ethmozin level (r = .59 $p < 0.01$) and average 1 hour plasma ethmozin

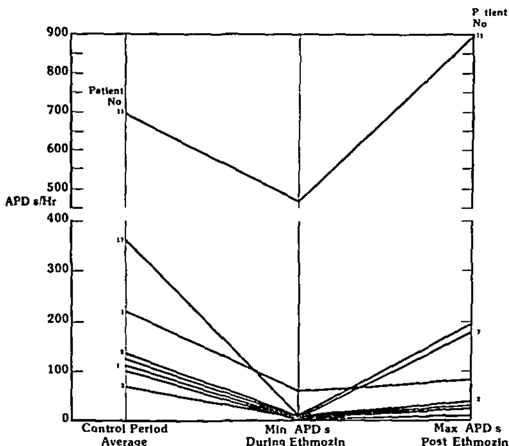


Fig 3 The frequency of atrial premature depolarizations (*APDs*) during each protocol period is displayed for individual patients The minimal (*min*) daily frequency of APDs is plotted during ethmozin therapy and the maximal (*max*) daily frequency of APDs is plotted during the post ethmozin placebo period Dose for each patient (mg /Kg) referenced by number in *Table I*

levels (25 49 73 97 121 145 hrs) (r = 65 p < 0 01)

Elimination half life could not be determined with accuracy due to the relatively infrequent blood samplings for ethmozin levels chosen in this study In five healthy volunteers after an oral dose of 500 mg of ethmozin the mean elimination half life was 4 hrs ± 1 hr (SD) with a range of 2 1 to 5 1 hrs The relationship between ethmozin dose plasma concentrations and efficacy is depicted in Table IV Patients with APDs responded at lower dose and plasma concentrations of ethmozin compared to those patients with VPDs The peak plasma levels after the first dose of ethmozin in patients No 4 to 17 (constantly dosed with ethmozin for 7 days) were reached at 1 hour in all cases except in two patients (Nos 5 and 14) and averaged 442 ± 47 (SE) (ng /ml) The maximum plasma level was reached between day 2 and day 6 during ethmozin dosing and was 597 ± 48 ng /ml with a range of 244 to 1300 ng /ml

Discussion

This first clinical study of ethmozin in the United States has demonstrated ethmozin to be a well tolerated effective antiarrhythmic agent Physicians in the Soviet Union have used ethmozin in doses up to 225 mg /day side effects of nausea epigastric distress dizziness and headache have been reported but are rare In the current study higher doses of ethmozin (up to 750 mg /day) have been used without adverse effects No adverse alterations in electrocardiographic hematologic or blood chemistry parameters were observed

The pharmacokinetics of ethmozin in man have not been fully defined In this study a trend was noted relating ethmozin dose to plasma level and to antiarrhythmic efficacy but these relations were not strong Ethmozin is well absorbed and appears not to be excreted in its native form in either feces or urine While we assume that the drug undergoes biotransformation the exact nature of these metabolites is not known nor is it

Table III Effect of ethmozin on ventricular premature depolarizations (VPDs) individual patient results

Patient No	Control mean VPDs per hour	% change from control during ethmozin			
		Mean change		Maximum decrease	
		Arithmetic	Logarithmic	Arithmetic	Logarithmic
2	143	+20	+90	−54	−8
4	360	−5	−41	−51	−68
5	48	−70	−87	−100	−100
6	539	−40	−47	−62	−67
7	1306	−4	−6	−30	−32
8	414	−64	−91	−87	−98
9	685	−100	−100	−100	−100
10	187	−39	−47	−64	−71
12	115	+22	+42	−62	−49
13	65	−69	−78	−100	−100
14	231	−75	−81	−89	−91
15	516	+4	−9	−58	−60
16	88	−71	−68	−87	−81
17	58	−78	−87	−96	−94

(p < 0 05)
Wilcoxon sign rank test for statistical significance ( ) was employed only for the mean logarithmic change data. In all other columns, a change of >60 should be used to consider reductions statistically significant. See text for details

clear whether they possess antiarrhythmic activity themselves Since plasma levels of ethmozin are measured in ng/ml and are thus tenfold less than those of other antiarrhythmic agents (measured in µg/ml) either ethmozin metabolites are biologically active or intact ethmozin is more potent than these other agents

It is important to note that patient characteristics and renal function both play a role in ethmozin pharmacokinetics Thus while we have noted a mean elimination half life of 4 ± 1 hours (range 2 1 to 5 1 hours) following a single 500 mg oral dose in young healthy men studies in cardiac patients with arrhythmias have demonstrated prolongation of mean elimination half life to 10 ± 3 hours (range 6 4 to 13 1 hours) in the presence of normal renal function and to 47 5 hours in one patient with renal insufficiency (Gilbert McMahon M D Ph D personal communication) Thus ethmozin elimination appears to be different in patients than in healthy subjects and this difference cannot be completely explained by associated abnormalities in renal function similar findings have been reported with other antiarrhythmic agents

Ethmozin appears to suppress both atrial and ventricular arrhythmias in ambulatory patients with non life threatening arrhythmias over a wide range of hourly frequencies Thus APDs were suppressed in about [illegible] per cent of our patients at relatively low ethmozin doses and plasma level While suppression of VPDs was less striking a comparably low drug doses and appeared t require higher ethmozin doses and plasma level approximately 70 per cent of our patients wit VPDs did respond favorably to therapy Th effective dose of oral ethmozin for VPD suppre sion remains to be determined but may approac 15 mg/Kg/day while 5 to 10 mg/Kg/da appears sufficient for suppression of APDs Th oral dosage regimen of ethmozin every 8 hou was shown to be effective but the potentia benefit of a loading dose to achieve efficacy earl in the first day of therapy required further tes ing

In testing the efficacy of an antiarrhythm agent, the methods used to quantify the arrhytl mia and the statistical techniques whereb arrhythmia frequency during drug therapy compared to a period without therapy are of grea importance Long term Holter monitoring patients with cardiac arrhythmias has demo strated great spontaneous variability in the hou ly frequency of both APDs and VPDs [illegible] addition the degree of reduction in arrhythm required to exceed that expected based c random chance varies with the length of both th control and treatment periods We have foun that a decrease of greater than 60 per cent in VP frequency was necessary to achieve statistic

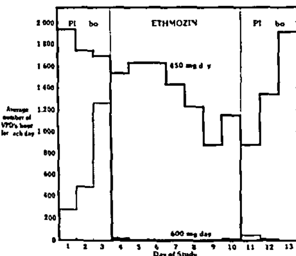


Fig 4 The frequency of ventricular premature depolarizations (VPDs) in patient No 9 are displayed during two different dose levels *The heavy black line* depicts the VPD frequency during 400 mg per day dosage of ethmozin with the accompanying pre and post placebo periods *The bar graph* demonstrates the VPD frequency at 600 mg per day of ethmozin *(solid bars)* with the accompanying pre and post ethmozin placebo periods *(stippled bars)* VPD data from the final placebo day at this latter dosage is not available due to equipment malfunction

significance when 3 days of control observations and 7 days of therapy data are available[7] as used in the current study In addition we have evaluated different techniques for comparing drug therapy to control data When the outcome of therapy was expressed as the percentage of all patients studied who showed a significant decrease in arrhythmia no difference in outcome was noted regardless of whether arithmetic or logarithmic techniques were used and regardless of whether the period of therapy was considered as all 7 days of drug therapy as only the final 5 days or as only the final 2 days of ethmozin treatment A higher response rate was noted in APD (but not in VPD) analysis when the maximal change rather than the mean change was used

Several important questions remain unanswered First does the favorable influence of ethmozin therapy on both atrial and ventricular arrhythmias in patients *without* life threatening disturbances of cardiac rhythm also pertain to patients with more malignant life threatening arrhythmias? Second are the higher doses of ethmozin apparently needed to suppress VPDs well tolerated in larger numbers of patients over longer periods of times? Third is ethmozin more effective than other agents in suppressing arrhythmias? Although further studies are needed to answer these questions it is clear that currently approved antiarrhythmic agents are limited by their relatively high rates of side effects by their need to be taken frequently (every 3 to 6 hours) or both Such limitations make long term patient compliance difficult With an increased emphasis on the elimination of arrhythmias as a means of preventing sudden death an antiarrhythmic agent that can be taken orally as infrequently as three times a day and that causes few if any side effects at doses that are effective would be a valuable addition to the therapeutic armamentarium Our results suggest that ethmozin may be such an agent

Table IV Relationship between daily dose of ethmozin plasma level and antiarrhythmic effect

	Daily dose of ethmozin		Mean daily dose	Mean plasma drug level	% Hourly arithmetic change during ethmozin from control	
	mg /Kg	No	mg /Kg	ng /mL	Mean	Max
VPDs	2 4 to 4 9	6	3 7	262	+10	−27
	5 0 to 6 9	7	6 0	409	−46	−69
	7 0 to 11 2	5	8 4	4,0	−61	−85
APDs	2 4 to 4 9	5	3 3	157	−46	−74
	7 0 to 11 2	4	8 9	489	−31	−96

N = Number of patients dosed at the level shown
= Mean of the plasma ethmozin concentration one hour after dose

Summary

Ethmozin a phenothiazine derivative was developed in the Soviet Union as a new antiarrhythmic agent We evaluated ethmozin using a controlled single blinded in hospital protocol in 14 ambulatory patients with ventricular ectopy ranging from an average of 48 to 1 801 depolarizations per hour and in eight patients with atrial ectopy ranging from 63 to 693 depolarizations per hour Placebo was administered for the first 3 days followed by ethmozin from 2 4 to 11 2 mg /Kg /day administered orally every 8 hours for 7 days and concluding with placebo for the final 3 days Continuous 24 hour long term electrocardiographic monitoring for 13 days was employed to measure drug efficacy accurately Six of eight (75 per cent) patients with atrial ectopy and 10 of 14 (71 per cent) patients with

Table III Effect of ethmozin on ventricular premature depolarizations (VPDs) individual patient results

Patient No	Control mean VPDs per hour	% change from control during ethmozin			
		Mean change		Maximum decrease	
		Arithmetic	Logarithmic	Arithmetic	Logarithmic
2	143	+20	+90	−54	−8
4	360	−[illegible]	−41	−51	−68
5	48	−70	−87*	−100	−100
6	539	−4[illegible]	−47	−62	−6[illegible]
7	1306	−4	−6	−30	−3[illegible]
8	414	−64	−91	−87	−98
9	68[illegible]	−100	−100	−100	−100
10	187	−39	−47	−64	−71
12	115	+22	+42	−62	−49
13	65	−69	−78	−100	−100
14	231	−75	−81	−89	−91
15	516	+4	−9	−58	−60
16	88	−71	−68	−87	−81
17	58	−78	−87	−96	−94

($p < 0.05$)
Wilcoxon sign rank test for statistical significance ( ) was employed only for the mean logarithmic change data. In all other columns, a change of >6[illegible]% should be used to consider reductions statistically significant. See text for details.

clear whether they possess antiarrhythmic activity themselves. Since plasma levels of ethmozin are measured in ng/ml and are thus tenfold less than those of other antiarrhythmic agents (measured in μg/ml), either ethmozin metabolites are biologically active or intact ethmozin is more potent than these other agents.

It is important to note that patient characteristics and renal function both play a role in ethmozin pharmacokinetics. Thus while we have noted a mean elimination half life of 4 ± 1 hours (range 2.1 to 5.1 hours) following a single 500 mg oral dose in young healthy men, studies in cardiac patients with arrhythmias have demonstrated prolongation of mean elimination half life to 10 ± 3 hours (range 6.4 to 13.1 hours) in the presence of normal renal function and to 47.5 hours in one patient with renal insufficiency (Gilbert McMahon, M.D., Ph.D., personal communication). Thus ethmozin elimination appears to be different in patients than in healthy subjects and this difference cannot be completely explained by associated abnormalities in renal function; similar findings have been reported with other antiarrhythmic agents.

Ethmozin appears to suppress both atrial and ventricular arrhythmias in ambulatory patients with non life threatening arrhythmias over a wide range of hourly frequencies. Thus APDs were suppressed in abou[illegible] per cent of our patients at relatively low ethmozin doses and plasma levels. While suppression of VPDs was less striking at comparably low drug doses and appeared to require higher ethmozin doses and plasma levels, approximately 70 per cent of our patients with VPDs did respond favorably to therapy. The effective dose of oral ethmozin for VPD suppression remains to be determined but may approach 15 mg/Kg/day while 5 to 10 mg/Kg/day appears sufficient for suppression of APDs. The oral dosage regimen of ethmozin every 8 hours was shown to be effective but the potential benefit of a loading dose to achieve efficacy early in the first day of therapy required further testing.

In testing the efficacy of an antiarrhythmic agent the methods used to quantify the arrhythmia and the statistical techniques whereby arrhythmia frequency during drug therapy is compared to a period without therapy are of great importance. Long term Holter monitoring of patients with cardiac arrhythmias has demonstrated great spontaneous variability in the hourly frequency of both APDs and VPDs. In addition the degree of reduction in arrhythmia required to exceed that expected based on random chance varies with the length of both the control and treatment periods. We have found that a decrease of greater than 60 per cent in VPD frequency was necessary to achieve statistical

Blood pressure reductions during self-recording of home blood pressure

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Home blood pressures have been recommended as a method to obtain more reliable and valid data on patients average blood pressures prior to making treatment decisions[1] Yet little has been published about the effect of the knowledge of daily blood pressure on patients One of the common objections to home blood pressure recordings is that patients might be made anxious by knowledge of their own blood pressure thus causing it to increase Studies using home blood pressures however have not identified adverse psychological reactions[3,4] In fact two investigators reported that most of their subjects felt reassured by taking their own blood pressures[3,5]

Another possibility is that home blood pressure readings by patients may have a positive treatment effect Carnahan and Nugent investigated this point but failed to control for or to report medication changes thus their findings (7 5 mm Hg decrease of systolic and no decrease of diastolic blood pressure) cannot be accepted as evidence related to this issue Several other investigators have mentioned blood pressure decreases while subjects were taking home blood pressures[7] but did not publish data on the magnitude of decreases

The purpose of the present study was to investigate the effects of a month of home blood pressure readings taken by patients with borderline to moderate hypertension Blood pressure data are analyzed separately for subjects who did not change medications The relationship of subject variables to blood pressure change is also examined

Methods

Subjects Ten subjects were selected from a Veterans Hospital outpatient clinic and 50 from volunteers who had previously been receiving treatment for their high blood pressure at other clinics or with private physicians Exclusion factors were as follows (1) diastolic blood pressure less than 90 mm Hg at the clinic or less than 88 mm Hg at home if the patient was not currently on antihypertensive medication (2) secondary hypertension (3) history of psychotic behavior or drug abuse (4) use of medications other than hypotensive drugs which might affect blood pressure as a side effect (5) hearing problems (6) lack of cooperation in taking home blood pressures on a regular basis or repeated nonattendance at the hospital s hypertension clinic (7) a raw score of 10 or less on the Abstraction section of the Shipley Hartford Scale This scale is a short test of intellectual abilities and the exclusion eliminated approximately the lowest 5 per cent of the population in abstraction abilities

Of the subjects excluded 16 had home blood pressure readings by the end of the second week which were clearly in the normotensive range in spite of continuing clinic diastolic readings greater than 90 mm Hg Twenty subjects were excluded because they were not reliable in returning for appointments and/or in providing home blood pressure data

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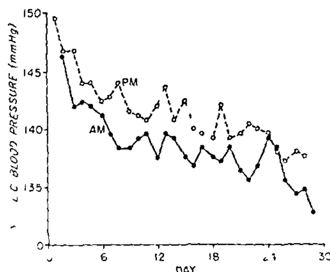


Fig 1 Systolic A M and P M blood pressure changes by day over a four week period for subjects without medication change Subjects began taking their blood pressures in the evening of Day 1 and took three readings each morning and evening

Fifteen female and five black subjects were included in the otherwise white male population Average age was 47 6 years with a range of 28 to 65 years Educational level ranged from the fifth grade through four years of graduate school with a mean of 14 5 years The average initial clinic blood pressure (mean of three readings ±S D) was 153 0 ± 20 0 mm Hg systolic and 99 4 ± 8 4 mm Hg diastolic Forty five of the 60 subjects were on medication for their blood pressure

Apparatus Each subject was provided with an aneroid sphygmomanometer and a simple diaphragm stethoscope Four subjects used large adult cuffs because of larger arm size All aneroid meters were checked for accuracy by comparing them to a mercury meter[9] at each subject s systolic and diastolic range Errors were noted and were used later to correct the blood pressure data

Procedures Subjects were scheduled for four appointments during the month of the study in order to check progress in taking home blood pressures These appointments were independent of regular medical appointments although home blood pressure data was made available to the physician to use in making medication decisions During the first appointment subjects were taught to take their own blood pressure readings In order to avoid a blood pressure increase due to squeezing the sphygmomanometer bulb [9] the cuff was placed on the left arm and subjects used the right hand to inflate the cuff while keeping the left hand and arm relaxed If a subject was left handed or had higher readings on the right side the sides for cuff and bulb were reversed The stethoscope diaphragm was held in place by slipping it partially under the edge of the cuff We found as have other investigators[11] that slight variations in the placement of the stethoscope diaphragms did not noticeably affect the blood pressure readings Readings were taken in a sitting position and diastolic was recorded as the disappearance of sound (fifth phase) Instructions and practice continued until subjects acquired confidence and familiarity with taking their own blood pressures In addition instruction sheets were provided for subjects to take home to remind them of advice related to maintaining high intra subject reliability[12] Subject s knowledge and skill were checked again during subsequent appointments

Concurrent blood pressure readings taken by each subject and the experimenter during every clinic appointment assured high inter subject reliability Reliability was considered adequate if the subject and experimenter had readings within 5 mm Hg of each other for both systolic and diastolic pressures The majority of subjects however had differences less than 3 mm Hg and no subjects had differences greater than this regularly Neither experimenter nor subject had knowledge of each other s readings at the time each judgment of blood pressure was made

Subjects recorded three blood pressure readings twice a day The time of the readings remained the same throughout the study, usually before breakfast and before dinner Subjects who were on medication also noted on their data sheet each day when they took their medication

Statistical analysis Daily A M and P M blood pressure readings were averaged separately for each subject For each of the four measures systolic and diastolic for A M and P M the data were fit with a second order or quadratic curve For the individuals who changed their medications during the course of the study the curve was fit to the data up to the day of medication change The value of the quadratic equation at the first day was subtracted from the value of the equation at the last day or day of medication change and was divided by the number of days to arrive at an estimate of the change per day The reason for using the change per day value rather

than a change value based on the first and last days only was to reduce the variability of the estimate by using all the available data

Standard t tests[11] were used to evaluate the significance of the difference of mean change per day values from zero This was done separately for subjects with and subjects without medication changes Product-moment correlation coefficients[3] measuring the relationship between change per-day and a number of other subject variables are presented for all 60 subjects because the data were the same for subjects with and without medication changes Blood pressure variability is defined as the standard deviation about the mean

Results

Blood pressure changes during the month of home blood pressure readings During the course of home blood pressure measurements there was an over all decrease in the mean blood pressure of the participants Figs 1 and 2 depict the mean systolic and diastolic values for A M and P M separately for the 37 individuals who did not change medication during the month Subjects began taking their blood pressures in the evening of Day 1 Decreases were greatest for the first day or two Blood pressure values however do not appear to have become asymptotic by the end of the month and some subjects whom we continued to follow showed decreases into the second month.

The figures show clear differences between A M and P M readings for systolic ($t = 3\ 318$ $p < 001$) but not for diastolic The blood pressure decrease was not significantly different for A M versus P M readings

Of the 23 individuals who changed medication 17 decreased their medication and six increased their medication If these subjects are included up until the point of medication change the curves in Figs 1 and 2 change only slightly the shapes are the same but the average values are lower with a slightly larger average decrease with time

The average change per day values are shown in Table I All average decreases for systolic and diastolic A M and P M are statistically significant

In order to determine the number of subjects who showed a clinically important decrease in blood pressure during the month of home readings the average of 12 readings for the last two days was subtracted from the average of the 12 readings for the first two days for subjects who did not change medication Responders defined as those having a decrease of systolic and/or diastolic blood pressure ≥ 10 mm Hg included 16 or 43 per cent of the 37 subjects Only two subjects had blood pressure increases ≥ 10 mm Hg both for systolic blood pressure only Of the 23 subjects who changed medications 10 subjects or 43 per cent were also responders during this same time period in spite of the fact that 17 of the 23 decreased medications

Because there was an initial sharp decrease in blood pressure we evaluated the decrease after

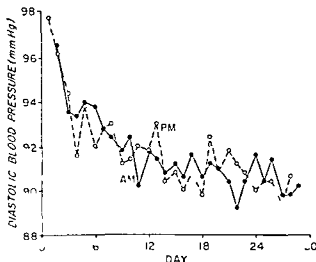


Fig 2 Diastolic A M and P M blood pressure changes by day for subjects without medication change

Table I Average blood pressure change per day until medication change or end of study*

Blood pressure measure	Change per-day	
	All 60 subjects	*37 subjects with no medication change*
Systolic AM	− 31 ± 07‡	−.23 ± 08†
PM	−.28 ± 08‡	−.29 ± 09†
Diastolic AM	− 19 ± 04‡	− 15 ± 05†
PM	− 17 ± 05†	− 17 ± 06†

Table entries are means ± SEM in mm. Hg A negative change-per-d y value indicates the estimated decrease of blood pressure per day for the 4 weeks f th tudy

†$p < 0\ 01$ as compared to zero change-per-day (two-sided t test)

‡$p < 0\ 001$ (t test)

Table II Average clinic blood pressure readings on the days of the four clinic visits*

Visit	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
1	154 8 ± 3 1	99 9 ± 1 2
2	150 2 ± 2 7†	96 4 ± 1 1‡
3	146 0 ± 2 2§	93 4 ± 1 0§
4	147 4 ± 2 6‡	94 2 ± 1 2§

Table entries are means ± SEM for the 49 subjects for whom data were available on all four visit days Three blood pressure readings were averaged for each subject for each clinic visit Average blood pressure readings on visit days 2 3 and 4 were significantly lower than those on day 1 with probability values as indicated

†p 05
‡p 005
§p 001

Table III Correlations between the change per day in blood pressure and other variables*

	Change per day (mm Hg)			
	Systolic		Diastolic	
	AM	PM	AM	PM
Initial clinic blood pressure	−44§	−35‡	−37‡	−18
Initial home blood pressure	−43§	−50§	−38‡	−31†
Age	−17	−27†	−10	−21
Home blood pressure variability	−37	−41‡	−35‡	−14

All 60 individuals were used in the calculation Table entries are the product moment correlation coefficients The initial blood pressures and blood pressure variability correlate systolic with systolic and diastolic with diastolic Home blood pressure variability is the standard deviation of the individual's home blood pressure readings.
†p < 01
‡p < 0 01
§p 0 001

the first two days using the same definition of responder Thirteen or 35 per cent of the 37 subjects were responders between Days 3 and 4 and the last two days There were three subjects during this period who showed an increase of 10 mm Hg or more two for systolic and one for both systolic and diastolic This latter subject was followed while continuing on home blood pressures an additional twelve months He maintained the blood pressure increase requiring a medication increase four months later By the end of the year however while still taking home blood pressures he had again reduced both his blood pressure and his medication

Clinic blood pressures also decreased during the month of home readings Values for the four visit days are shown in Table II The decrease was about the same from visits 1 to 2 as from visits 2 to 3 There was no further decrease for visit 4 The differences between the means for visits 1 and 3 are statistically significant for both systolic ($t = 3\ 68$ $p < 001$) and diastolic ($t = 5\ 58$ $p < 001$) The same pattern of clinic blood pressure decrease occurred from one visit to another when only those subjects who did not change medication were considered Decreases were observed from visits 1 to 3 and there was not a mean decrease from visits 3 to 4 The mean systolic decrease to the third appointment was 3 9 mm Hg ($t = 1\ 66$ $10 > p > 05$) and the mean diastolic decrease for the same period was 5 5 mm Hg ($t = 4\ 16$ $p < 001$)

Factors correlated with change per day The change per day values for A M P M systolic and diastolic combinations were examined for relationships to sex Veterans Administration status (whether or not the subject had been a regular VA Hypertension Clinic outpatient prior to the study) level of medication age educational level, abstraction score initial clinic blood pressure initial home blood pressure and blood pressure variability The only significant associations were with initial clinic and home blood pressures age and blood pressure variability (see Table III) Partial correlation coefficients controlling for initial home blood pressure level revealed that age and home blood pressure variability did not correlate significantly with change per day independent of initial home blood pressure level

Discussion

In the present study there were no deleterious effects on blood pressure because of anxiety due to subjects knowledge of their own daily blood pressure levels Instead there was a blood pressure decrease The decrease was clinically important (systolic and/or diastolic decrease ≥ 10 mm Hg) for 43 per cent of the 37 subjects who had no medication change during the four week period This percentage is if anything an underestimate because we excluded 16 subjects from the study whose diastolic pressures at home without medication dropped below a mean of 88 mm Hg during the first two weeks

The decrease in clinic blood pressure was not necessarily related to the decrease in home blood pressure Clinic pressures are a measure of reactivity to the clinic environment and this reactivity may decrease even when the average blood

pressure remains the same Conversely the reactivity may remain the same when average daily home blood pressures decrease For example decreases in home blood pressures have been observed in drug trials when clinic pressures have not decreased[14,16]

Possible explanations for blood pressure decreases Possible explanations for these observed blood pressure decreases include (1) placebo effects and/or increased compliance associated with change of treatment program (2) increased attention of health care practitioners (3) habituation of blood pressure to the conditions of measurement and (4) biofeedback effects These possibilities are considered in the following discussion

1 Change of treatment program and increased compliance Non VA patients were started on both the home blood pressure program and regular medical treatment at the Hypertension Clinic at the same time Their change per-day values were not statistically different from those of patients who had already been in ongoing medical treatment at the VA Clinic Change of medical treatment was therefore probably not a placebo factor It is of course possible that since both groups were in a research program this resulted in increased attention to such factors as salt intake and exercise Improved medication compliance however did not appear to affect the results since there were not statistically significant differences in change per day between the 15 subjects who were not taking any medications and those who were on hypotensive drugs

2 Attention If increased compliance with non pharmacological medical advice was a factor related to blood pressure decrease it may have been due at least in part to the increased attention subjects received during the additional appointments related to home blood pressures The increased attention may also have contributed to a feeling of well being or security which in turn affected blood pressure level

3 Habituation Subjects who were cuff responders (reacted with blood pressure increases to the process of having their blood pressures measured) may have shown a decrease in blood pressure as their cuff responses became habituated Subjects may also have initially experienced a defense reaction as a result of the added effort and/or anxiety associated with taking their own blood pressures Again as they became accustomed to the measurement process the defense reaction would habituate These two types of habituation are the most likely explanation for the initial steep drop of blood pressure during the first day or two of home blood pressure readings

4 Biofeedback Biofeedback or feedback information about physiological processes may result in blood pressure decreases due to subjects direct control over their blood pressure or as a result of indirect control The latter consists of covert or overt behavior changes which in turn affect the physiological variable In our interactions with subjects it was not unusual to get reports of changes in activities or interpersonal interactions due to subjects observations of relationships between certain variables and blood pressure Some of these variables were exercise social events salt intake caffeine intake temperature amount of sleep or rest and amount of leisure time Our favored hypothesis is that increased awareness and attention given by subjects to non pharmacological factors were the most important antecedents of the blood pressure decrease which occurred after an initial habituation process (first day or two)

Self recording of blood pressure another behavioral treatment? The blood pressure decreases which we observed in this study were in the same range as those which have been observed after relaxation or biofeedback therapies[1,18] As with the relaxation therapies the blood pressure decreases were greater for subjects with higher blood pressures An advantage of home blood pressures over other behavioral treatments is the ease with which they are employed In the absence of negative effects of home blood pressures the possibility of their value as a direct treatment tool certainly adds support for increasing their use

Need for a longer period of blood pressure assessment Regardless of whether patient s self measurement of blood pressures at home is effective in reducing average blood pressures our data indicate that in cases where there is no immediate risk it is important to wait for a settling down period before home blood pressures are used to make treatment decisions In spite of a greater number of readings than are taken in the clinic the waiting period for some patients may extend for at least a month

Summary

Blood pressure readings were taken at home twice a day for one month by 60 subjects with essential hypertension The average change per day value based on quadratic curves fit to each subject s data (for the entire month or to the day of medication change) was negative and was statistically significant for both systolic and diastolic and for A M and P M readings Clinically significant decreases in blood pressure, defined as systolic and/or diastolic decreases $\geq$ 10 mm Hg from the first two to the last two days occurred in 43 per cent of the subjects

The observed blood pressure decreases may have been due to (1) placebo effects and/or increased compliance associated with the change of treatment program (2) increased attention of health care practitioners, (3) habituation of blood pressure to the conditions of measurement or (4) biofeedback effects The most likely explanation for the initial blood pressure decrease in habituation The smaller but continuing decrease after the first two days was probably due at least in part to a biofeedback effect If further studies support such an hypothesis then home blood pressure readings should be used on a wider scale for treatment purposes They are easier to administer than other behavioral treatments and the observed decreases appear to be of the same order of magnitude

Regardless of the treatment potential of this type of biofeedback the decreases in home blood pressures while patients are taking their own pressures daily at home suggest the importance of a diagnostic waiting period until blood pressure stabilizes and before pharmacological treatment is prescribed This period may last a month or longer for some patients

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Cardiovascular malformations in the fetal alcohol syndrome

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The fetal alcohol syndrome (FAS) first described by Jones and Smith[1,2] in 1973 includes cardiovascular anomalies In a survey of the recent literature describing cases of FAS[3] 46% exhibited cardiac abnormalities but cardiac catheterization and angiocardiographic diagnoses were rare

We have recently had the opportunity to evaluate two infants with FAS in our catheterization laboratory and found septal defects in association with hypoplastic pulmonary arteries in both

Case Reports

Case No 1 A. B was the 909 gram black male product of a 28-week gestation to a 22 year old gravida 2 para 2 with a documented long history of chronic daily excessive alcohol intake (exact amount not recorded) The initial neonatal course included a poor suck and frequent opisthotonic posturing Features characteristic of the FAS included microcephaly flattened nasal bridge bilateral ptosis and hypertelorism

Congestive heart failure was first noted at two months of age. A Grade 3/6 harsh holosystolic murmur was heard at the left mid-sternal border Chest x ray showed massive cardiomegaly with pulmonary vascular congestion The ECG revealed an axis of +90 degrees with biventricular hypertrophy Treatment with digitalis and diuretics was instituted

Cardiac catheterization documented a large muscular ventricular septal defect with a large left to right shunt and pulmonary hypertension (Table I) Of particular interest was the associated angiographic finding of dysplastic pulmonary arteries (Fig 1)

Because of a poor response to medical management surgical closure of the ventricular septal defect was carried out with prompt control of his cardiovascular symptoms A 2 centimeter defect at the level of the attachment of the septal leaflet of the tricuspid valve was patched Peripheral stenosis of the right pulmonary artery was also noted The child presently 2½-years-old is doing well with only mild symptoms related to his microcephaly

Case No 2 T P a black female was the 2,830 gram product of a term pregnancy to a 26-year old gravida 3 para 3 mother a heroin addict with a documented ethanol intake of 1 liter/day Head circumference was 33 cm Facies characteristic of the FAS were noted including bilateral ptosis, short palpebral fissures prominent forehead and jaw with maxillary hypoplasia and bilateral epicanthal folds

At 3 weeks of age signs and symptoms of congestive heart failure developed A Grade 3/6 harsh holosystolic murmur was audible at the left lower sternal border and a Grade 2/6 systolic ejection murmur was audible at the left base A grade 2/6 decrescendo diastolic murmur was intermittently heard at the left lower sternal border Massive cardiomegaly with pulmonary overcirculation was seen on chest x ray ECG showed an axis of −150 degrees and biventricular hypertrophy Congestive heart failure persisted despite maximal doses of digoxin and diuretics.

Cardiac catheterization revealed a partial atrioventricular canal with a large left-to-right atrial and ventricular shunt A 52 mm Hg systolic gradient was recorded between the right and main pulmonary arteries (Table I) Angiography demonstrated small and dysplastic pulmonary arteries Moderate aortic insufficiency was also noted

Because of the failure of medical management pulmonary artery banding and ductal ligation were carried out At surgery the main pulmonary artery was noted to be [illegible] than the aorta though the branch pulmonary arteries [illegible] described as "normal in size" She is now 2¼ years-old [illegible] remains well from a cardiovascular standpoint The [illegible] insufficiency murmur no longer exists She is presently considered for operative repair

The child is mildly retarded developmentally and [illegible] ently institutionalized in a chronic care facility du[illegible] unstable family situation

Discussion

The excessive consumption of alcohol [illegible] been considered to be detrimental to th[illegible] oping fetus Jones and Smith[1] in 1973 [illegible] the first series of infants with multiple [illegible] attributed to the intake of ethanol and [illegible]

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Abnormal mitral valve motion associated with ventricular septal defect following acute myocardial infarction

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The appearance of a systolic murmur following an acute myocardial infarction raises the spectre of a serious structural lesion. The differential diagnosis includes ruptured ventricular septum, ruptured papillary muscle, and papillary muscle dysfunction. The distinction between these conditions is often difficult to make. There have been several reports in the literature expressing the potential usefulness of echocardiography in diagnosing a ruptured ventricular septum.[1] Similarly, there have been several descriptions of the echocardiographic appearance of a flail mitral valve or torn chordae. The present case demonstrates a situation in which the clinical impression and echocardiogram were at odds and cardiac catheterization was required to make the correct diagnosis.

Case report

E. L., a 69-year-old woman, presented to Montefiore Hospital with a five-day history of progressive dyspnea on exertion and fatigue. She denied any history of arteriosclerotic or rheumatic heart disease and had no prior knowledge of a heart murmur. Her past medical history was unremarkable.

On physical examination the patient was a thin, pale female in mild respiratory distress. Her blood pressure was 90/60 mm. Hg and her pulse was 96/minute. There was neck vein distention and bilateral rales. The point of maximum intensity was in the sixth intercostal space 4 cm. left of the mid-clavicular line. There were both left and right ventricular heaves and a palpable systolic thrill along the left sternal border. P was increased and there was an S gallop. A grade 5/6 holosystolic murmur heard over the entire precordium radiated into the axilla.

The admission electrocardiogram revealed sinus rhythm, new small q waves in Leads V to V, and nonspecific ST-T wave changes in the anterior precordial leads. Serial electrocardiograms and enzyme determinations following admission were unchanged.

An echocardiogram was performed with the patient in the supine and left lateral decubitus positions using Irex equipment and a 2.25 MHz transducer focused at 7.5 cm. The aortic valve was normal and the left atrium and right ventricle were mildly enlarged. The initial movement of the posterior leaflet of the mitral valve during diastole was in a posterior direction. This was followed by a distinctive motion of the leaflet characterized by both coarse and fine fluttering (Fig. 1) throughout diastole. This pattern previously has been observed in patients with a flail posterior leaflet. The anterior leaflet appeared to move normally and the E-F slope and thickness were also normal (Fig. 1). The septum moved normally and no defects were appreciated. The left ventricle was mildly dilated (3.5 cm./M.) however the calculated ejection fraction and V were normal (68 per cent and 1.3 circ./sec., respectively). Based on this study it appeared that the patient had a flail posterior mitral leaflet with acute mitral regurgitation. Because of her continued unstable condition it was decided to treat the presumed mitral regurgitation with unloading agents. During insertion of a balloon-tipped catheter to monitor right-sided hemodynamics, oxygen saturations were obtained and were 43 per cent in the right atrium, 72 per cent in the right ventricle and 71 per cent in the pulmonary artery. The systemic arterial oxygen saturation was 97 per cent. Pressure data revealed a right atrial mean pressure of 13 mm. Hg, right ventricular pressure of 57/16 mm. Hg and a mean pulmonary capillary wedge pressure of 23 mm. Hg with A and V waves of 24 mm. Hg. These data were consistent with a left to right shunt at the ventricular level. The patient was initially treated with nitroprusside. Subsequently dopamine was added in an attempt to stabilize her condition.

Despite aggressive medical therapy the patient's condition

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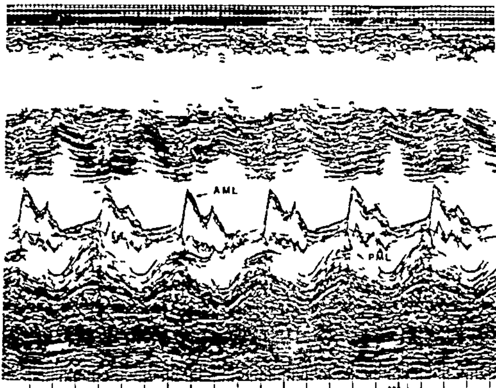


Fig 1 Echocardiogram demonstrating coarse and fine fluttering of the posterior leaflet (*PML*) of the mitral valve in diastole Abbreviation *AML* = anterior mitral valve leaflet

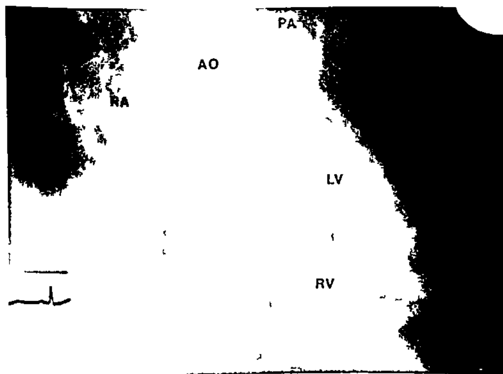


Fig 2 Left ventriculogram in the right anterior oblique projection demonstrating filling of the right ventricle (*RV*) through an apparent ventricular septal defect There was no evidence of mitral regurgitation Abbreviations *RA* = right atrium *PA* = pulmonary artery *Ao* = aortic root *LV* = left ventricle

slowly deteriorated In view of these circumstances a left heart catheterization was performed to establish the diagnosis in preparation for possible emergency surgery Left ventriculography confirmed the presence of the previously diagnosed ventricular septal defect (Fig 2) and the absence of mitral regurgitation The right ventricle was markedly dilated and functioned poorly The left ventricle was mildly enlarged and revealed akinesis of the apex and anterior septum and hypokinesis of the anterolateral wall The remainder of the ventricle was hyperkinetic The left ventricular end diastolic pressure was elevated to 30 mm Hg and the left ventricular ejection fraction (in the right anterior oblique projection) was 82% Coronary angiography demonstrated triple vessel disease including a total occlusion of the left anterior descending coronary artery after the first septal perforator

The patient was taken to the operating room where a 2 cm ventricular septal defect immediately anterior to the posteromedial papillary muscle was repaired with a Teflon patch There were areas of fresh infarct surrounding the ventricular septal defect and in the left ventricular apex The mitral valve and its apparatus were inspected and found to be intact and there was no mitral regurgitation The three diseased vessels were bypassed However the patient could not be weaned from the pump oxygenator and died in the operating room

Discussion

Structural defects associated with acute myocardial infarction represent both a diagnostic and therapeutic dilemma The murmur of an acquired ventricular septal defect can often be differentiated from that of acute mitral regurgitation Classically the murmur of a ventricular septal defect is located along the left sternal border and is associated with a palpable thrill, while the murmur of acute mitral insufficiency is more often located at the apex radiates into the axilla and lacks an associated thrill However as demonstrated by Selzer and colleagues in their series of 10 patients with acquired ventricular septal defects the murmur may often be loudest at the apex or of equal intensity at the apex and left sternal border and may radiate to the axilla Similarly the presence of a precordial thrill has been shown to be present in only 50 to 60 per cent of patients with acute ventricular septal defects in most series Therefore, one realizes that clinical differentiation between these two lesions may be extremely difficult For many years the only way to distinguish between these disorders was cardiac catheterization and angiography Therefore echocardiography would be an attractive means of making this distinction and would provide a more easily accessible tool for establishing the diagnosis

The initial report in the literature by Chandraratna and associates proposed that echocardiography could be used to make the diagnosis of ruptured ventricular septum The authors described findings of a dilated right ventricle and an unusual pattern of mitral valve motion characterized by complete closure of the valve after its initial opening early in diastole and then by the reopening of the valve Subsequent reports have appeared describing other echocardiographic features felt to be helpful in the diagnosis of a ventricular septal defect The report by DeJoseph and co workers described a particular pattern of abnormal septal motion while that of Silverman and colleagues[1] stressed prominent motion of the tricuspid valve and reversal of direction of its E F slope All of these findings were absent in the present case

In the case reported above the clinical picture (i e new holosystolic murmur with a palpable thrill and absence of pulmonary edema) was most consistent with a ruptured ventricular septum Yet the echocardiogram strongly suggested the presence of mitral regurgitation secondary to a flail posterior mitral leaflet The diagnosis was finally made by the use of bedside right heart catheterization and was subsequently confirmed by left ventriculography and surgery

Thus the echocardiographic pattern of coarse mitral leaflet fluttering previously thought to be diagnostic of a flail mitral leaflet can be seen with a ruptured ventricular septum in the absence of mitral valve pathology Wood has described torrential flow through the mitral valve associated with ventricular septal defects Capp and associates[11] have demonstrated a pattern of persistent blood flow through large ventricular septal defects during isovolumic relaxation and diastole The combined effect of these two factors probably accounts for turbulence within the left ventricle during diastole The proximity of the ventricular septal defect to the posteromedial papillary muscle in addition to the turbulence may explain the abnormal mitral valve motion Therefore one must be cautious in interpreting this particular pattern since it may be seen with either a ventricular septal defect or a flail mitral leaflet Mitral valve fluttering may represent a non specific echocardiographic finding associated with conditions in which turbulent flow is present within the left ventricle

One must question the use of echocardiography as a diagnostic tool in the differentiation of a new systolic murmur in patients with acute myocar

dial infarction The previous studies[1] and this one collectively show a lack of uniform and specific diagnostic echocardiographic criteria for acute ventricular septal defects On the other hand bedside right heart catheterization provides a simple method for distinguishing ventricular septal defect from acute mitral regurgitation with a high degree of accuracy and should be relied upon for this differentiation

Summary

It is often difficult to make the clinical distinction between acute mitral regurgitation caused by papillary muscle dysfunction or rupture and ventricular septal defect complicating an acute myocardial infarction A case of a patient with rapidly progressive congestive heart failure and a loud murmur is presented Echocardiography strongly suggested the presence of a flail posterior mitral leaflet However the patient was subsequently found to have rupture of the interventricular septum This diagnosis was made with bedside right heart catheterization and was later confirmed by left ventriculography and direct inspection at the time of surgery The mitral valve apparatus was completely normal Thus this case demonstrates the apparent lack of specificity of the accepted echocardiographic criteria for flail mitral leaflet and acutely ruptured interventricular septum and the potential necessity of cardiac catheterization to distinguish between these entities

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Review

Low renin hypertension A current review of definitions and controversies

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Suppression of plasma renin levels is frequently encountered in patients with hypertension[1] Low plasma renin concentration is also one of the characteristic features of primary aldosteronism but the incidence of this identifiable disorder in the general hypertensive population is now believed to be quite low Thus the mechanism for renin suppression in the vast majority of patients with low renin hypertension (LRH) has remained obscure and controversial although one cannot exclude the possibility of early primary aldosteronism in some of these patients Several reviews and discussions[1] of LRH attest to the interest in this subject There have been some recent developments which make review of this area with emphasis on the mechanism and treatment particularly timely

Incidence

The incidence of LRH has varied in different reported series from as low as 9 per cent to as high as 50 per cent[6] The wide variation in incidence probably reflects many factors such as the age and race of the hypertensive and control populations studied the nature of the stimuli used to define the patients the selection of patients and the method of renin measurement

The stimuli utilized to provoke renin responses have varied and included salt depletion by a low salt diet and/or a diuretic acute hypotension induced by sodium nitroprusside or diazoxide the use of hydralazine and exercise Considerable variability has existed in the techniques of sodium depletion by dietary means or by diuretics These varying stimuli may elicit quantitatively different responses or involve different mechanisms for renin release Brunner and associates have used a nomogram based on the relationship of 24 hour urinary sodium excretion to plasma renin activity obtained in the upright posture

It is probable that patients with LRH may not respond similarly to different stimuli[9] There is limited knowledge about the reproducibility of the same stimulus in the normal and hypertensive subjects[1 ° ●]

The sensitivity of the assay for renin measurement may be yet another variable[10] Early studies used bioassay techniques and in recent years radioimmunoassay has been used because of enhanced assay sensitivity and specificity Irrespective of these variables most investigators agree that the incidence of LRH in an unselected hypertensive population is between 20 to 30 per cent[5-7]

Effects of age sex and race

In most studies[15] but not in all[4 4] it has become evident that both basal and stimulated levels of plasma renin decline with age in normal and also in hypertensive subjects[1] Although in some reports LRH patients have been older than other patients with hypertension[° 5] precise information about the age and composition of the patients and the control populations is hard to find in other reports In one recent study the incidence of LRH in the young hypertensive patients using appropriate age-matched controls was 18 per cent Female subjects seem to have lower plasma renin responsiveness than males[•] It is now also generally accepted that black subjects have lower plasma

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renin levels than whites[17] The reason for this difference is unclear but it may be genetic[21] Recent studies suggest that total body sodium in blacks may be higher than in whites[2] or that they may handle sodium loads differently It is therefore evident that in defining patients with low renin hypertension one must take into account all the above mentioned variables to establish the appropriate controls and normal ranges in determining the renin status of a specific hypertensive subject The stimulus used for eliciting the renin response must be well standardized, and the reproducibility of the response in the control population should be demonstrated before applying the technique to hypertensive populations The control population should be sufficiently large and representative of the hypertensive population studied to enable valid comparisons Although we cannot be dogmatic protracted stimulation such as with low sodium diet rather than short term stimulation with diuretics may be preferable for defining low renin patients for research purposes unless studies using both methods are shown to be comparable in stimulating renin in the same control population. The short term method is of course more convenient and may be acceptable for therapeutic purposes if one wants to use renin typing for treatment

Relationship of low renin to duration and degree of hypertension

Since renin suppression could be mediated by a baroreceptor mechanism the magnitude and duration of hypertension may be important Chronically elevated blood pressure may alter the functional status of the juxtaglomerular apparatus In one study[1] no correlation was observed between the duration of hypertension and renin suppression but in this and another report[1] there was an inverse relationship between diastolic blood pressure and plasma renin activity Messerli and colleagues[3] noted that their patients with LRH had higher blood pressure than those with normal renin But such relationships are not very clear-cut in other studies

Serum and urinary electrolytes and renal function

Serum electrolytes potassium in particular have not been reported to be consistently abnormal in LRH Patients with LRH reported by Messerli and associates had slightly lower mean serum potassium levels than hypertensives with normal renin Others have commented about overt hypokalemia in a majority of their patients[4,7] Some hypokalemic LRH patients had adrenal adenoma upon adrenal exploration[4,2,3] Thus the extent and incidence of electrolyte abnormalities in patients with LRH is far from clear and confounded by the inclusion of patients with apparent aldosteronism among the LRH population There is even less information on urinary electrolytes or renal function Gross renal abnormalities have not been reported in LRH suggesting no alteration of renal hemodynamics in most studies

Proposed mechanisms of renin suppression

1 **Arguments in favor and against the role of a mineralocorticoid** A major part of the thrust in the investigation of the mechanism of LRH has been directed at the identification of a mineralocorticoid since LRH has been assumed to be due to hypervolemia based on indirect evidence

There have been several reasons why mineralocorticoid excess has been implicated in this form of hypertension First since primary aldosteronism is associated with suppression of renin and since both the hypertension and hyporeninemia could be explained by increased mineralocorticoid activity of aldosterone LRH has been thought to have a similar mechanism by analogy Secondly patients with LRH have been found to benefit from therapy with agents known to cause volume depletion or to counteract mineralocorticoid effects Inhibition of steroidogenesis by aminoglutethimide has also resulted in a reduction of blood pressure in LRH[30] Finally measurements of body fluid or sodium spaces appear to indicate that there was indeed an increase in some of these parameters in LRH[30,3] Based on the premise that LRH is due to the effects of mineralocorticoids causing both renin suppression and elevation of blood pressure investigations have proceeded along several lines

There are two pieces of evidence suggesting that LRH is a volume dependent form of hypertension Woods and associates[30] noted that the exchangeable sodium was increased in LRH when compared to hypertensives with normal renin responses The total blood volume and plasma volume were not different Jose Crout and Kaplan[3] measuring plasma volume and extracel

lular fluid volume in hypertensives found that the mean extracellular fluid volume was greater in patients with LRH

Additional indirect support for the alleged mineralocorticoid participation in LRH has been gathered from other studies The salivary sodium-potassium ratio which is known to be influenced by adrenal mineralocorticoid hormones was observed to be lower in LRH[33 32] and an enhanced natriuresis either during low sodium intake or after saline infusion has been reported in several studies[33 34 41] These latter results have been interpreted by some to represent increased sodium stores in the body or a state of hyperexpansion of body fluid compartments Finally a less specific argument has been advanced for a role of salt retaining hormones by the pharmacological responses to various agents in patients with LRH The effect of these drugs will be discussed subsequently in the context of therapy of LRH

A Role of mineralocorticoid other than aldosterone If the evidence for the effects of a mineralocorticoid hormone has been limited the identification and unequivocal proof of its role has been even more elusive The quantitative estimates of urinary and plasma aldosterone have been normal in LRH Therefore a search for other steroids in LRH has proceeded with great fervor Since hypertension is known to occur in adrenal 11 β hydroxylase or 17 α hydroxylase deficiency desoxycorticosterone (DOC) secretion excretion and plasma concentration have been examined Abnormal levels have been found in only a small number of patients[27 35] In a few reports abnormal ratios of steroids in some patients with LRH have suggested the possibility of an incomplete 11 hydroxylation or 17 hydroxylation defect [3] Two cases of hypertension and low plasma renin activity have been recorded in association with adrenal adenomas which appeared to be secreting 18 OH DOC *in vitro* or DOC *in vivo*

The presence of unusual steroids has been reported in LRH One of the predominant steroids secreted by the rat adrenal is 18 hydroxy 11 deoxycorticosterone (18 OH DOC) A role for 18 OH DOC in certain forms of experimental hypertension in rats has been suggested[3 0] Although the human adrenal gland was known to be capable of producing it *in vitro* only recently the secretion of this hormone in human blood has been demonstrated Melby and associates[41 42] raised considerable hopes of a breakthrough in the understanding of the mechanism of LRH when they observed elevated urinary 18-OH DOC excretion rate in some patients with LRH High levels were obtained in the adrenal venous effluent when compared to normal subjects

In view of the ACTH dependence of 18 OH DOC secretion dexamethasone suppression was attempted in some patients[42] resulting in both reduction of 18 OH DOC excretion rate and lowering of blood pressure In two patients blood pressure became normal after bilateral adrenalectomy Since in these patients the only identifiable steroid abnormality was increased excretion of 18 OH DOC a causal role for the latter was immediately suggested Even though earlier investigations have suggested significant mineralocorticoid activity for 18 OH DOC[4] and there was a recent report of its hypertensive effect rats [3] it is now regarded that this steroid h relatively weak salt retaining potency[44] In addition its low affinity for binding to renal mineralocorticoid receptors[45] further makes it an unlike contender for the hypothetical steroid Othe have found increased plasma levels of 18 O DOC not only in LRH but also in patients wi hypertension and normal plasma renin [4 7] Uh and colleagues[48] have not found evidence increased 18 OH DOC in a small number patients with LRH

Hopes were rekindled with the discovery of tw new steroids Melby and Dale found that th adrenal tissue of patients with LRH converted greater proportion of 18 OH DOC to 16 α 1 dihydroxy DOC than adrenals removed fro patients with breast cancer This compoun when given to rats potentiated the sodiu retaining effect of aldosterone At the same tim Liddle and Sennett[50] observed that in the urine their LRH patients 16 β hydroxy dehydroepia drosterone (16 β OH DHEA) and its related fo mer were present in rather large quantities The steroids were also noted by the same group have significant mineralocorticoid activity adrenalectomized rats Subsequently however further studies seem to have dispelled any role fo these steroids In their most recent repor Liddle s group has reported normal levels of 1 β OH DHEA in LRH as have others[51 52] I addition Gomez Sanchez and co workers[53] wi unable to substantiate the biological activity the compound using two different rat bioassa

systems. In short term experiments 16 β OH DHEA failed to induce hypertension when given to rats.[33] Further Funder and associates[34] noted that 16 β OH DHEA had variable biologic activity in different rats but found that irrespective of the biologic effect the affinity of the steroid for the renal mineralocorticoid receptors was quite low They also noted that Melby s steroid (16 α 18-dihydroxy DOC) did not enhance the binding of aldosterone to the receptors and they could not confirm the potentiating effect of this compound as originally suggested [5]

B Role of aldosterone Gunnells and co workers[23] noted that several of their patients with low renin hypertension and normal aldosterone excretion rate had an adrenal adenoma on surgical exploration and observed improvement of hypertension following surgery Earlier Conn and associates [9] had reported about the presence of normokalemic primary aldosteronism Based on these and other observations Grim and co workers[59-61] have raised the possibility that aldosterone itself may be incriminated in LRH They have argued that if renin suppression is taken to be a response to extracellular fluid volume expansion or increased sodium stores a normal level of plasma or urinary aldosterone could be considered inappropriate Grim[5] observed that the plasma aldosterone concentrations were similar in their low renin and normal renin hypertensives and hence demonstrated a higher ratio of plasma aldosterone per unit of plasma renin activity in LRH A similarly abnormal relationship has been reported by others [6 63 129] A decreased metabolic clearance rate of aldosterone could not be shown to be responsible by Brown and colleagues[43] in their LRH patients Increased adrenal sensitivity to angiotension or ACTH has also been proposed in LRH to explain the enhanced mineralocorticoid response in the face of low renin levels

Grim and Shade [0] proceeded further to examine the validity of their hypothesis that normal aldosterone levels were inappropriate in LRH They administered small doses of DOCA to three normal subjects and noted a lowering of plasma and urinary aldosterone and plasma renin activity in these subjects Since DOCA invoked renin suppression was similar to that seen in LRH but with concomitant suppression of plasma aldosterone levels they proposed that the presence of a normal plasma aldosterone level in LRH reflects an abnormality of the physiological suppression of aldosterone and therefore represents some degree of autonomy in aldosterone secretion It is of interest that Collins and co workers[64] earlier noted that many patients with hypertension failed to suppress aldosterone secretion normally following a sodium load suggesting an abnormality of aldosterone control in hypertension Some of the patients of Grim and associates[5] with LRH underwent adrenal exploration and were found to have bilateral adrenal hyperplasia These observations led to the hypothesis that LRH may represent an early stage in the evolution of primary aldosteronism [6] There are other reports of surgically proven aldosteronoma in patients with normal urinary aldosterone excretion rate [5] Although the possibility of early hyperaldosteronism cannot be discounted in all patients with LRH it appears unlikely since many patients with LRH have normally suppressible aldosterone excretion rates or plasma aldosterone concentrations [70] The studies of Hollifield and colleagues as discussed subsequently seem to discount a primary role for aldosterone in elevated blood pressure of LRH since pharmacologic blockade of aldosterone production did not result in a reduction of blood pressure in such patients but did reduce blood pressure in patients with classical primary aldosteronism It is possible that the inappropriate plasma aldosterone concentration in LRH reflects increased adrenal sensitivity to angiotensin [65] and hypertension may not be related to such an effect

The possibility of mineralocorticoid excess as the cause of LRH still exists since the combined mineralocorticoid activity of plasma steroids or urinary mineralocorticoid activity appears to be greater in LRH [71] than in normal renin hypertension Ulick and associates[72] seem to have found another steroid metabolite in the urine of a juvenile patient with LRH which has not been clearly characterized The role of other potential but as yet unidentified steroids has been proposed [73 7] This area remains under active investigation at many centers

The crux of the postulate that LRH is a mineralocorticoid hypertension has revolved around the demonstration of alterations of body sodium or volume and the observation of a greater therapeutic response with volume depletion

*Since the submission of this rticle the paper by Wisg rhof M and Brown R D Increased adrenal sensitivity t angiotensin II in low renin essential hypertensi n J Clin In est 61 1456 1978 has appeared, furthe supporting the earlie bservati n of Taylo and associates.[65]

in steroidogenesis Recent studies from Scotland and the Netherlands dispute such a thesis[75,76] Brown and associates[77] failed to substantiate any evidence of expanded plasma volume exchange able fluid volume or sodium in LRH a finding which differed from the same measurements in *their patients with primary aldosteronism* How ever the lack of sufficient sensitivity in the existing methods of measuring body fluid and electrolyte compartments and the influence of other factors make it very difficult to resolve the contradictory findings at this point

Baxter and colleagues[7] measuring plasma mineralocorticoid binding activity to renal miner *alocorticoid receptors, failed to detect any signif* icant differences in the mean binding activities between plasma from normal subjects normal renin and low renin hypertensives but noted significantly increased activity in the plasma of patients with primary aldosteronism

Aldosterone and other mineralocorticoid hor mones tend to increase urinary kallikrein excre *tion and in the usual cases of essential hyperten* sion kallikrein excretion rate is lower than in normal subjects In such context it is of interest that excessive urinary kallikrein excretion was not found in LRH when compared with normal renin hypertensives[79]

2 Arguments in favor or against other mech anisms Since convincing evidence for mineralo corticoid mediation of LRH is lacking other possible mechanisms have to be considered

A High dietary sodium intake The specula tion about higher sodium intake in the patients with LRH is unlikely Adlin and colleagues[8] investigating the dietary history and urinary sodi um on regular home diet of their patients with hypertension were unable to find any statistical difference in urinary sodium excretion between hypertensives with normal or low renin levels

B Role of sympathetic nervous system The role of the sympathetic nervous system in LRH has been examined Although the measurements of urinary catecholamines and metabolities have been grossly normal some of the abnormal clinical effects of diazoxide induced hypotension have been construed as evidence of diminished sympathetic activity Collins and associates[1] reported that LRH patients had a subnormal rise in urinary norepinephrine on standing Esler and co workers[81] noted good correlation between the increment of plasma renin activity and that of urinary norepinephrine on standing and in LRH patients a lower concentration of plasma norepi nephrine was seen In addition blunted responses to stimulating maneuvers were also observed in the LRH group But Pool and colleagues[83] failed to find any difference in plasma norepinephrine *levels between normal subjects normal renin* and low renin hypertensives Even if sympathetic dysfunction is demonstrated it may be extremely difficult to prove that it is the cause and not the effect of LRH

C Possible alteration of renin release or generation of angiotension in vivo An inverse relationship between plasma renin concentration *and renal filtration fraction was noted* by Schal ekamp and associates[86] who suggested a barore ceptor mediated renin suppression The possibili ty of increased body potassium in renin suppres sion seems to have been ruled out[87] Likewise normal body potassium observed in that study argues against a mineralocorticoid etiology There is no evidence of reduced renin substrate concentration in LRH[85] The possibility of an inhibitor of the renin-renin substrate reaction cannot be excluded However the reactivity of added renin to the plasma of LRH patients in some earlier studies did not seem to be reduced[89] On the other hand Brooks and co workers recently reported that the renin reactivity in a small group of patients with LRH was indeed reduced Since prostaglandin A (PGA) is capable of inhibiting the renin-renin substrate reaction such a possibility was excluded when the measured plasma PGA level was actually noted to be lower in LRH as compared to normal controls and patients with normal renin hyper tension

D Role of prostaglandins It has recently been shown that indomethacin administration atten uates the plasma renin *response to* furose mide,[91] suggesting that renal prostaglandin may be involved in the renin response Kraloff and colleagues[3] observed that the infusion of prosta glandin A_1 caused the greatest fall in blood pressure and increase in sodium excretion in LRH patients as compared with other hypertensive groups These results can be construed as *evidence of a possible* prostaglandin deficiency in LRH Brooks and associates[90] recently reported a lower prostaglandin A level in plasma in a small number of LRH patients compared to normal subjects and hypertensives with normal renin

E Role of heterogeneous forms of renin Still other possibilities for LRH may be worth considering Abnormal or inactive forms of renin have been described in certain conditions [98, 9] and more recently Boyd[100] has reported the presence of proportionately greater amounts of acid activatable renin in LRH Weinberger and associates[101] found no increase in inactive renin but rather a suppression of total plasma renin concentration in their LRH patients In view of the inherent differences in methodology and the complex nature of such studies satisfactory resolution of this aspect will need further careful investigations

F Possible renal abnormality Brown and co workers[7] having failed to find any evidence of excess of body fluid or sodium in LRH proposed a renal functional abnormality for renin suppression. They hypothesized that the phenomenon of pressure-natriuresis which is shifted to the right in hypertension becomes irreversibly reset in LRH probably explaining the decreased plasma renin level in relationship to sodium balance

Swales[0] suggested that renin suppression may be related to nephrosclerosis resulting in reduced arteriolar distensibility and therefore attenuation of baroreceptor sensitivity But it is difficult to conceive how such a mechanism can explain the failure of dietary or diuretic induced sodium depletion to stimulate renin release which is believed to occur through the mediation of the sodium sensing macula densa region of the renal tubule Furthermore there is no radiological or pathological evidence of any difference in the renal arterioles in LRH compared to other forms of hypertension Finally LRH has been considered as an artifact related to declining plasma renin level with age since bimodality of distribution in plasma renin in a hypertensive population could not be demonstrated[1] Even if one accepts a mechanism of renin suppression other than that mediated by a mineralocorticoid the mechanism of hypertension probably has to be explained on a different basis Since the low renin state is known to occur also in diabetes mellitus lead intoxication and with overuse of licorice it may be important to rule out such possibilities in the usual case of LRH

Prognostic significance

In animal experiments renin or angiotension II has been known to produce cardiovascular injury[106, 10] There are also similar lesions reported in humans in the presence of high catecholamine or angiotensin II levels[1] Interestingly Brunner and co workers observed a low incidence of myocardial infarction or strokes in their patients with LRH as compared with other hypertensive groups There has been both support for[109, 110] and skepticism about these findings[111, 113] Christlieb and associates[1] probably have provided a more realistic interpretation—that renin as a risk factor must be considered in concert with other risk factors Since most antihypertensive drugs alter the plasma renin level it is far from clear what the relevance of the original renin typing to the subsequent course of the patient may be

Management

As mentioned earlier most therapeutic approaches in LRH have been directed at the premise that the low plasma renin and the hypertension are due to mineralocorticoid induced salt retention and volume expansion Woods and associates[1] attempted to reduce the hypothetical adrenal mineralocorticoid with aminoglutethimide In LRH there was a greater decrease in blood pressure than in normal renin hypertension Similarly the blood pressure response to spironolactone a known mineralocorticoid antagonist has been used by a number of investigators [6, 2] to indicate a steroid mediated form of hypertension in such patients Spark and Melby[116] presented enthusiastic results with high dose spironolactone therapy and attempted to demonstrate some degree of specificity of response in LRH Earlier Jose and colleagues[31] however had not found any difference in response in LRH compared to normal renin hypertensives using a smaller dose and shorter duration of therapy Carey and co workers[11] conducting a double blind study and Adlin and associates[18] in another study confirmed the beneficial effects of spironolactone as did Crane and Harris Adlin and colleagues[1] and others [121, 1] using either spironolactone or hydrochlorothiazide demonstrated significant and comparable blood pressure responses by both agents again implying volume dependence of the hypertension in LRH More recently Vaughn and associates[23] have further shown the therapeutic value of volume depletion using either chlorthalidone or spironolactone (even with a lower dosage of the spironolactone than used in the earlier reports) in LRH

However in this latter study almost half of the patients with LRH did not respond to either regimen Brooks and co workers[124] and studies from Europe have further supported the conten tion Uchida and colleagues[120] and Spark and associates[1] have reported restoration of renin levels to 'normal following normalization of blood pressure with spironolactone Spark and associates[121] noted that there was a greater hypo tensive effect and increment in plasma renin level with spironolactone than with hydrochlorothia zide and an inverse relationship between the renin and the blood pressure changes They suggested that the restoration of normal renin response was mediated by blood pressure reduc tion rather than volume depletion since the diur esis by either regimen was comparable Two recent studies[5,6] have questioned the useful ness of renin typing for specific therapy

Melby and associates[12] having demonstrated *18 OH DOC excess in their LRH patients admin* istered dexamethasone with blood pressure reduc tion in four out of five patients In two patients bilateral adrenalectomy normalized the blood pressure Brown and colleagues in Glasgow observed no reduction in blood pressure with dexamethasone in their LRH patients with elevated plasma DOC levels but the treatment might not have been long enough The hypoten sive effect of high doses of spironolactone in these patients with correction of hypokalemia was considered presumptive evidence for a role for excessive DOC secretion In these cases however as reported subsequently[5,6] the measurements of extracellular fluid volume or sodium space did not show an increase of those parameters raising doubts as to the relevance of elevated DOC concentration to the pathogenesis of low renin and hypertension in these patients

Hollifield and associates[9] have treated patients with LRH and primary aldosteronism with aminoglutethimide and a metyrapone dexameth asone combination on separate occasions Inter estingly the results demonstrated that blood pressure could be lowered in both LRH and primary aldosteronism with aminoglutethimide Metyrapone dexamethasone lowered blood pres sure only in primary aldosteronism and not in LRH Urinary mineralocorticoid activity similar ly was reduced by aminoglutethimide in both groups but by metyrapone dexamethasone only in primary aldosteronism These observations have been interpreted to mean that a mineralo corticoid originating prior to the step involving 11 β hydroxylation is responsible for LRH These studies further tend to absolve aldosterone as playing a role at least in a population of LRH patients

In conclusion direct evidence for mineralocor ticoid mediation of LRH has yet to be presented in the vast majority of patients Even when elevated levels of other steroids are found a causal role must be established Therapeutic modalities based on the presumption of volume excess have been successful but cannot be consid ered specific It may very well be that LRH is a heterogeneous group of different entities due to different etiologic factors somewhat similar to Nugent s classification[1] A plea can be made for the establishment of a uniform method of catego rizing LRH in order to understand the nature of the disorder comprehensively

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Fundamentals of clinical cardiology

Prevention of ventricular rhythm disturbances in patients with acute myocardial infarction

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The interaction of research and clinical practice is well exemplified by the Coronary Care Unit in which since its inception[1,2] great efforts have been directed towards reducing mortality from life threatening rhythm disturbances following acute myocardial infarction The prompt diagnosis of any instability of heart rhythm combined with a logical but aggressive approach to prevention and management have all resulted in lessening mortality during the early dangerous days following infarction Equally important however is the recognition that the highest mortality occurs within the first few hours following the attack usually a result of ventricular fibrillation of which the acutely ischemic myocardium is especially prone even when the actual extent of infarction may be relatively small Since the majority of CCU admissions occur later than these first critical hours the net effect CCUs have had on the total mortality of acute myocardial infarction is less than might otherwise have been expected This fact has resulted therefore in the creation of special teams to manage acute rhythm disturbances before the patient is transferred to hospital

To better understand the current approaches to acute dysrhythmia prevention and management a brief summary of the basic underlying electrophysiology follows

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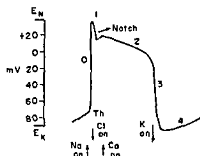


Fig 1 Action potential (schematic) of a conducting Purkinje ventricular fiber *Th* = threshold *0* = upstroke *1* = rapid repolarization *2* = plateau *3* = final repolarization *4* = diastolic repolarization

Applied electrophysiology

The extracellular fluid bathing the exter surface of the cardiac cell membrane may considered to be the positively charged plate capacitor and the cytoplasm of the int surface of the cell membrane the negati charged plate These two plates are separa the molecular structure of the membrane which serves as the dielectric Since pot can leave the cell in excess of its anion it is responsible for generating the voltage di across the capacitor Events of the cardiac potential are brought about by a re dis of charge altering the resting state microelectrode is used to record electrical within the cardiac cell the resting brane voltage is measured at mV (Fig 1) This is determined potassium conductance and potassium equilibrium potential IV of the depolarizing cycle the voltage approaches threshold and the

becomes permeable to sodium ions The entry of sodium ions is controlled by electrically charged gates conceptually classified into an m or activation variable and an h gate the inactiva tion variable On reaching threshold and as the gates assume an open position allowing sodium ions to enter rapidly the action potential elicits the spike of phase 0 the height of which approxi mates a sodium equilibrium potential reaching to about +20 mV Sodium permeability lessens at this point and the membrane becomes more permeable to chloride ions which on entering the cell begin to repolarize it A small second inward current is carried by both sodium and calcium ions using a different membrane channel during the plateau period of the action potential and probably playing an important role in cardiac contraction Following this potassium and chlo ride ions start moving out of the cell tending to repolarize it and gradually the outward potas sium current rises and supercedes the smaller inward currents which diminish thus causing the final phase of repolarization

Potentially lethal ventricular rhythm disturbances

Following acute myocardial infarction the patient is at risk of sudden ventricular rhythm disturbances which may be fatal even in the presence of only a small myocardial lesion The mechanism by which such life threatening dys rhythmias may be precipitated are as follows

1 **Re entry** For this to occur there needs to be a geometrically protected region through which the action potential can be conducted only slowly and adjacent to it muscle which having already repolarized can now be re excited In addition a unidirectional block is needed to sustain the consequent excitatory wave in a loop fashion

For some time electrophysiologists have pon dered the fact that to adequately explain the mechanism of re entry requires demonstrating the presence of a very slow conduction velocity which is localized to the injured area More recently it has been shown that the action poten tial from these regions may depend on slow inward current channels as well as on a depressed sodium channel These slow conduction systems have been demonstrated in the AV node but may also be functional in the ventricle itself if the fast channels are inactivated by pathological condi tions Any part of the conduction system or abnormal segments of ventricular muscle may therefore be the site of such loop circuits

2 **A rapidly discharging spontaneous or auto matic focus** This may be responsible for generat ing a ventricular dysrhythmia, particularly when the normal sinus mechanism has been suppressed by the diseased state The depolarized ischemic muscle may serve as a source of current to pacemaker cells in the Purkinje system acceler ating the speed with which the fiber reaches threshold Spontaneous pacemaker action may also develop in ischemic muscle if the cells are depolarized to a point which represents the threshold of the slow inward current channels

Bigger and associates[9] when studying the natu ral history and genesis of dysrhythmias used the Harris model[10] which involves a two stage occlu sion of the anterior descending coronary artery of the dog Focusing their attention on the fact that ventricular dysrhythmias become manifest in two phases they were able to show that the first or early phase starts immediately following ligation of the coronary artery and lasts for a few minutes thereafter and is then followed by a period of quiescence Some 6 to 9 hours later however a second and delayed phase of acute ventricular rhythm disturbances occurs and may persist for the next 48 hours

Clinical studies have described a pre hospital phase of extremely lethal dysrhythmias, and a mortality rate of 60 per cent during the first hour of myocardial infarction has been reported This highly lethal phase is followed by a later and usually in hospital phase over the next 3 to 4 days when the patient is prone to further ventricular dysrhythmias Relating experimental models to this clinical observation is still only speculative since a direct relationship has not as yet been demonstrated yet the animal model does provide the clinician with a certain amount of insight into the cause of events leading to life threatening ventricular dysrhythmias Furthermore it also permits a more rational plan to be developed for the prevention and management of these poten tially lethal acute rhythm disturbances

During the early stage following infarction ventricular cells are deprived of substrate and oxygen leading to a depletion of ATP Sodium and potassium transport become altered resulting in a loss of potassium and in an accumulation of sodium ions within the cell Local lactic acidosis with consequent pH changes follow and there is

an accumulation of potassium in the extracellular fluid as well as alterations in the sarcolemmal chemistry all of which contribute to a reduction in the resting transmembrane voltage and to a disruption of the fast sodium current Catechol amines which are released locally facilitate conduction through the slow channels Conduc tion in the ischemic region becomes slow and disorganized while electrical activity in the ischemic tissue persists when adjacent normal cells may have repolarized completely As a result ventricular premature beats tachycardia or even fibrillation may result In addition ischemia may sometimes promote repetitive depolarization of ventricular cells resulting in abnormal automaticity

Six to ten hours after coronary occlusion in the dog a second phase of dysrhythmias may be precipitated and corresponding cellular changes can be demonstrated in the subendocardial Purkinje fibers Progressive chemical changes can be followed over the next 24 hours mostly demonstrating an accumulation of lipid droplets in these fibers In addition Wit and Friedman[1] have shown that these cells also show a reduction in the maximum diastolic transmembrane volt a e action potential amplitude and the rate of phase 0 depolarization as well as spontaneous diastolic depolarizations Though not clearly established the suggested mechanisms include alterations of membrane conductance either an increase in gNa or gCa or possibly a decrease in gK It is also thought that the reduction in blood supply to the Purkinje *fibers leads to delayed* changes in these cells possibly explaining the tardy start of rhythm disturbances arising from this region of the myocardium Abnormal auto maticity in the Purkinje fibers are probably responsible for non paroxysmal ventricular tachycardia non coupled ventricular premature beats and accelerated idioventricular rhythms The duration of the action potentials of the infarcted tissue is prolonged and furthermore normal cells are found adjacent to ischemic cells in the region of the infarct Thus all the basic requirements which permit local re entry circuits to function are fulfilled

The two mechanisms of re entry and abnormal automaticity may also combine when a prema ture action potential from the border of an infarct is propagated into the infarcted zone itself with areas of altered conduction time and path–length precipitating a rapid re entrant rhythm Further investigations may well localize the electrophys iological cause of the early rhythm disturbances to different mechanisms including the involve ment of slow action potentials and drugs which block the calcium channel activity for example verapamil may prove highly beneficial in preventing and managing these early ventricular dysrhythmias More recently it has been suggested that there may be a neural origin to cardiac rhythm disturbances resulting from an increased sympathetic traffic during the acute phase of myocardial infarction

Antidysrhythmic drugs

A rational consideration of the use of drugs for the prevention and treatment of ventricular rhythm disturbances in association with myocar dial infarction is aided by a classification of their effects based on electrophysiological principles Recently Arnsdorf and Hsieh[11] have proposed such a classification

Group 1 Procainamide quinidine disopyra mide Cause decreased sodium conductance and reduce the velocity of conduction

Group 2 Lidocaine phenytoin Cause in creased potassium conductance decreased con duction velocity and depressed sodium conduc tance in ischemic tissues In addition they have central nervous system effects

Group 3 Propranolol tolamolol alprenolol metoprolol Produce beta adrenergic receptor blockade

Group 4 Bretylium tosylate Acts primarily through an anti adrenergic action but its precise electrophysiological effect is still unknown

Group 5 Verapamil Blocks calcium channel activity and is effective against slow responses

Despite the wide variation in accepted clinical practice an intravenous anti dysrhythmic drug is usually chosen from the list classified above Dysrhythmias which may warn of more serious and possibly lethal rhythm disturbances to follow include frequent ventricualr premature beats (more than 5 per minute) ventricular premature beats manifesting the R on T phenom enon and paired or multiform ventricular prema ture beats Runs of accelerating ventricular tachycardia may show progressive shortening of the R R intervals and spontaneous activity may be recorded before more dangerous sustained rhythms occur

Drug management

Step 1 As soon as warning rhythms have occurred intravenous lidocaine should be given in a dose of 20 to 50 µg/Kg /minute To achieve a rapid blood level an initial loading dose is essential and one or two intravenous injections of a bolus of 75 to 100 mg should be given A continuous intravenous infusion over many days may be maintained thereafter at a rate of up to 4 mg / minute Beyond that level very careful observation is needed to detect the earliest signs of CNS irritation which if they occur require immediate lessening of the administered dose

Step 2 Should lidocaine fail to adequately control the emerging ventricular premature beats or short runs of ventricular tachycardia a Group 1 drug should next be tried since lidocaine a Group 2 drug has now been shown to be ineffective or only partly successful Because intravenous quinidine may have undesirable effects both electrophysiologically and hemodynamically procainamide is usually chosen A loading dose of 0.5 to 1 G is given followed by an intravenous infusion of 1 to 4 mg /minute

Should procainamide alone fail to produce the desired effects it may be administered together with lidocaine to see whether such combined therapy will succeed Electrophysiologically this combination results in an increase in potassium conductance and in a decrease in sodium conductance helping to explain why the two together have an additive beneficial effect

Step 3 Should the combination of lidocaine and procainamide fail to control the rhythm disturbances the next group of drugs to be tried would be beta adrenergic blocking drugs of which propranolol has enjoyed the most widespread reputation in this country The immediate effects of beta adrenergic blocking drugs on the action potential is a small reduction in its duration and an increase in the diastolic depolarization of pacemaking fibers More recently Raine and Vaughan Williams have shown that prolonged treatment with propranolol results in a striking increase in the duration of the action potential which helps to suppress dysrhythmias since it increases the refractory period

Step 4 For dysrhythmias which remain extremely refractory to treatment drugs from Groups 1 2 and 3 can be combined but may result in profound myocardial depression Very careful monitoring of patients receiving this type of therapy is therefore essential

Step 5 Bretylium tosylate an anti dysrhythmic drug is now available for clinical use should be tried in resistant dysrhythmias since it may be effective not only in helping to control refractory ventricular premature beats and tachycardia, but it appears also to increase the threshold for ventricular fibrillation[1] It has been successfully used when all other measures have completely failed to defibrillate the ventricle or when temporary defibrillation has occurred the patient rapidly reverting to fibrillation

Verapamil[2] a calcium antagonist drug is as yet not available for general clinical use in this country, although reports from abroad indicate its beneficial effect particularly for the control of supraventricular and junctional rhythm disturbances

Additional anti dysrhythmic drugs are not yet in widespread clinical use in this country but results of their clinical trials here and abroad are available They include

A *Tocainide* a primary amine analogue of lidocaine which is available for intravenous and oral administration It has been shown to be effective in reducing ventricular premature beats at a plasma concentration ranging from 5 to µg/ml.

B *Mexiletine* another Group 1 anti dysrhythmic drug with local anesthetic effects has been found to control ventricular rhythm disturbances both experimentally and in clinical use The therapeutic range of the drug is relatively narrow (0 75 to 2 0 µg/ml) and its intravenous administration is associated with a high incidence of adverse effects

Step 6 If all drug administration has been found ineffective the use of a temporary pacemaker to overdrive and prevent the emergence of further ventricular dysrhythmias should be instituted without delay Pacing may begin by stimulating the atrium to deliver a stimulus which will pass down the AV node bundle of His bundle branches and Purkinje tissue in a normal sequence and furthermore the mechanical beats that are produced will retain the hemodynamic advantage of atrial systole

Endo and epicardial mapping of irritable foci in the ventricle with the intent of surgically removing a dysrhythmogenic focus is feasible but is beyond the scope of this review

Pre hospital management The risk of sudden death is highest at the onset of acute myocardial infarction[3] Although of obvious importance pre-

hospital trials of therapy are extremely difficult to conduct and control A double blind trial by Valentine and colleagues[11] of the use of 300 mg lidocaine intramuscularly suggested that there were fewer patients who died within two hours within the lidocaine group than in those receiving a placebo There were however many discrepancies in the randomization of patients vitiating the conclusions suggested by the authors More recently Barber and co workers[1] investigated the use of intravenous lidocaine 100 mgs over 2 minutes followed by 300 mgs intramuscularly in 12 patients and were able to show that a satisfactory plasma level of lidocaine can be achieved during the pre hospital phase

Apart from the choice of drug and the route of its administration two additional practical points need to be mentioned Patients may be given the drug who later are shown not to have had myocardial infarction thus making it even more difficult to assess the use of the drug in preventing ventricular fibrillation following acute myocardial infarction Others may inadvertently receive a drug even when a contraindication to its use is present and undesirable effects may follow Nevertheless the importance of properly conducted randomized trials to prevent sudden death in the pre hospital phase of acute myocardial infarction can hardly be over emphasized

Discussion

Apart from the correct choice of an antidysrhythmic drug alone or in combination other clinical parameters following acute myocardial infarction need to be carefully considered and adequately treated since they too may be important both in the genesis and in the continuation of ventricular rhythm disturbances Thus hypo or hyperkalemia hypoxia congestive cardiac failure abnormally high adrenergic drives hypovolemia or inappropriate tissue concentrations of digoxin must be recognized when present and if necessary corrected as promptly as possible Up to the present the results of trials to determine the efficacy of antidysrhythmic drugs following acute myocardial infarction have unfortunately shown no conclusive evidence that the incidence of acute mortality has been favorably affected Some of these trials have been heavily criticized because of their design since often no double blind controls had been used Bloomfield and colleagues did report a controlled double blind trial and showed that quinidine reduced the incidence of ventricular dysrhythmias in patients with uncomplicated myocardial infarction but they did not assess the effect of the drug on preventing primary ventricular fibrillation Reynell reported on the use of procainamide for the same purpose and Koch Weser and co workers who undertook a double blind study in 70 patients concluded that procainamide reduced the incidence of ventricular premature beats but that there was no statistically significant benefit in preventing primary ventricular fibrillation Snow reported favorable results using propranolol in a dose of 20 mg orally every 8 hours and suggested that there was a reduction in mortality during the first 28 days following acute myocardial infarction in patients treated this way but Balcon and co workers[11] who undertook a controlled double blind study of propranolol in the early days following myocardial infarction concluded that there was no definite lessened mortality A controlled multicenter trial of the use of propranolol[14] has supported these conclusions

The effect of low dose lidocaine (0 05 to 2 mg /minute) in preventing ventricular dysrhythmias has been studied by several investigators who were unable to demonstrate that prophylactic lidocaine had any effect in preventing primary ventricular fibrillation in the dose range administered It is important to recognize however that plasma levels in lidocaine were in general not available Furthermore these studies were designed to evaluate the effects of a variety of drugs in preventing primary ventricular fibrillation of which lidocaine was only one On the other hand lidocaine is usually successful in 80 to 90 per cent of cases in suppressing ventricular premature beats provided an adequate plasma level is achieved and its high dose administration (3 mg /minute) following an initial bolus of 100 mgs intravenously has been investigated The measured levels of lidocaine during the intravenous infusion were 3 5 to 4 2 μg/ml and both studies suggested that high dose lidocaine was effective in preventing primary ventricular fibrillation It should be noted however, that the over all mortality rate in the two series was similar in the treated and in the control groups

Conclusion

Up to the present time no absolute recommendation can be made regarding the efficacy of any drug alone or in combination for the preventi

and management of acute ventricular rhythm disturbances following myocardial infarction There is, however, enough evidence to indicate that prophylaxis with lidocaine might have considerable benefit in protecting the patient against ventricular fibrillation and that more detailed randomized controlled studies are required

Since all drugs which have anti dysrhythmic effects tend also to have side effects some of which are undesirable and serious their unnecessary use or their administration in concentrations higher than therapeutically needed should be avoided if at all possible

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Clinical pharmacology of the new beta-adrenergic blocking drugs Part 7 New horizons in beta-adrenoceptor blockade therapy Labetalol

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Ahlquist[1] has proposed that adrenoceptors consist of two distinct types which he termed alpha (α) and beta (β) and there is overwhelming experimental and clinical evidence in support of this concept Agonists acting at one or both types of adrenoceptor have been available for years However the situation with antagonists is different in that until recently only antagonists acting at α or β adrenoceptors but not at both were available Phentolamine is a typical α adrenoceptor antagonist and propranolol a typical β adrenoceptor antagonist In 1972 the pharmacology of a unique agent was described labetalol which had antagonist properties at both α and β adrenoreceptors [4] Labetalol has recently been approved for use in hypertension in Great Britain and represents the forerunner of a new pharmacological group of compounds with combined α and β adrenoceptor blocking properties

The clinical experience with labetalol is now being gathered worldwide in angina pectoris hypertension and arrhythmias with the first clinical trials beginning in the United States In this article the clinical pharmacology efficacy and toxicity of this promising new beta alpha adrenoceptor blocking agent will be described and its potential therapeutic applications will be discussed

Pharmacodynamic and pharmacokinetic properties (Table I)

Pharmacodynamic properties Labetalol 5-(1 hydroxy 2 [(1 methyl 3 phenylpropyl)amino] ethyl)salicylamide (Fig 1) is a competitive antagonist at both α and β adrenoceptors Over the range of *in vitro* and *in vivo* tests used labetalol has been shown to be 6 to 10 times less potent than phentolamine at α adrenoceptors 1 5 to 4 times less potent than propranolol at β adrenoceptors and was itself 4 to 16 times less potent at α than at β adrenoceptors [5] Labetalol blocked α and β adrenoceptor mediated sympathetic nerve stimulation to approximately the same extent as with exogenously administered phenylephrine or isoproterenol [5]

The β adrenoceptor blocking action of labetalol like propranolol is non selective [5, 6] It might therefore be expected that the drug would cause bronchoconstriction in asthmatic subjects as does propranolol [6] In animal studies labetalol has been shown to be four times less potent than propranolol in the heart but about 11 times less potent on the lung [5] If this applies clinically to patients with bronchial asthma then at equipotent doses labetalol should cause less bronchoconstriction than propranolol The α adrenoceptor blocking activity of labetalol might also be beneficial in asthmatic subjects since there is evidence that α adrenoceptors are present in bronchial muscle and that their activation causes bronchoconstriction In man α adrenoceptor antagonists may have a bronchodilator action of

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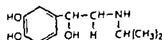
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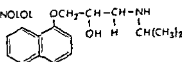
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Table I Pharmacological properties A comparison between propranolol and labetalol

Pharmacologic property	Propranolol	Labetalol
Beta blockade potency ratio (labetalol = 1)	1 5 – 4	1
Alpha adrenoceptor blocking effect	0	+
Cardioselectivity	0	0
Partial agonist activity	0	0
Membrane stabilizing activity	+	+
Extent of absorption (% of oral dose)	> 90	> 90
First pass hepatic metabolism	+	+
Dose dependent bioavailability	+	+
Lipid solubility	Strong	Weak
Active metabolites	+	−





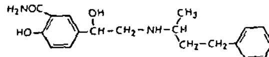


Fig 1 Structural formulas of the β agonist isoproterenol the β antagonist propranolol and the α β antagonist labetalol

their own and have been shown to enhance the bronchodilator actions of isoproterenol and salbutamol[8, 9]

In view of the ability of labetalol to block both types of adrenoceptor it was particularly important to resolve the question of its specificity The blocking action of labetalol both *in vivo* and *in vitro* has been shown beyond doubt to be specific for α and β adrenoceptors The drug has no antihistamine activity and probably lacks a direct vasodilator component[5] Vasodilators such as diazoxide characteristically reduce contractile responses of vascular muscle to a variety of spasmogens whereas labetalol reduces contractile responses to norepinephrine only[5]

Although labetalol is devoid of blocking actions at receptors other than adrenoceptors it does possess additional actions It has a direct negative inotropic action (unrelated to adrenoceptor blockade) probably a manifestation of membrane stabilizing activity a property shared by other β adrenoceptor antagonists (including propranolol) With this membrane stabilizing property it reversed ouabain induced arrhythmias However as with propranolol the direct negative inotropic effect (membrane stabilizing property) of labetalol is unlikely to be clinically important as this effect is apparent only at doses considerably higher than those required for α or β adrenoceptor blockade[5]

In animal experiments labetalol has been shown not to possess partial agonist (intrinsic sympathomimetic) activity at cardiac β adrenoceptors[2]

Pharmacokinetic properties (Table I) The absorption distribution and metabolism of labetalol has been studied in rat rabbit dog and man as part of the pharmocological toxicological and clinical evaluation of the drug

The plasma levels of radioactively labelled labetalol and high urinary excretion of radioactivity show that labetalol is well absorbed by man The drug has a first pass metabolism similar to that of propranolol so there may be a variation in bioavailability dependent on the dosage of drug administered

The drug is quickly taken up by the tissues and rapidly cleared from the body via both kidneys and the bile Labetalol is much less lipophilic than other beta adrenoceptor blocking agents and because of this there is neglibible uptake of labetalol in the brain However there is a reversible binding of the drug to the melanin of the uveal tract in the eye[1, 11]

Labetalol is metabolized in the liver by conjugation and the metabolites are excreted by the kidney (50%) and via the bile into the feces (50%) There is decreased metabolism of the drug in patients with hepatic disease necessitating lower dosage The pharmacokinetics of labetalol are being studied in patients with poor renal function

Peak serum levels of the drug are seen one hour after oral administration and the therapeutic blood level of drug has been found to be 5 $\mu g/ml$ in man[2]

Physiological and metabolic effects (Table II) Labetalol has α and β adrenoceptor blocking

Table II Hemodynamic effects of propranolol and labetalol*

Hemodynamic parameter	*Propranolol*	*Labetalol*
Resting heart rate	↓↓	↓ ↔
Exercise induced increment in heart rate	↓	↓
Peripheral resistance	↔ ↓	↓
Effect on blood pressure (rest)	↓	↓↓
Exercise induced increment in blood pressure	↓	↓↓
Cardiac contractility	↓	↓ ↔
Cardiac output	↓	↔ ↓
Effect on elevated plasma renin	↓	↓

*In dosages giving similar degree of beta blockade

properties both in man and animals There has been some difference in opinion between investigators concerning physiologic effects of labetalol because when a compound has a variety of properties the balance between those properties may change at different dose levels It may be that at low doses of labetalol β adrenoceptor blocking properties predominate whereas at higher doses α adrenoceptor blocking properties are the most significant The data concerning dose variable effects have not been obtained

The hemodynamic effects of labetalol are attributable to its adrenoceptor blocking actions In animal and human studies labetalol like propranolol reduced cardiac contractility an effect attributable to β adrenoceptor blockade Labetalol differed from propranolol in decreasing rather than increasing total peripheral resistance and in causing larger falls in resting blood pressure at equipotent β_1 adrenoceptor blocking doses[5] It seems reasonable to attribute these differences to peripheral vasodilation resulting from the vascular α adrenoceptor blocking action of labetalol At the same time, in exercising human subjects blood pressure increments seemed to be blocked to a greater degree than has previously been reported with propranolol probably because of the concomitant alpha adrenergic blockade [1]

At rest labetalol has been shown not to appreciably lower heart rate and left ventricular stroke volume in contrast to propranolol where both these parameters are attenuated and with phentolamine where they are increased The effect of labetalol on resting heart rate is most probably reflex in origin resulting from vagal withdrawal in response to the peripheral vasodilation mediated by alpha adrenergic blockade[5] In exercisin human subjects the increment in heart rate attenuated by labetalol similarly to propran lol[5]

The resting cardiac output has been shown no to appreciably decrease with labetalol[11] an effe which may be mediated by the vasodilating unloading effects of alpha adrenergic blocka in contrast to the decrease in this parameter se with propranolol (increased peripheral resistan due to unopposed alpha adrenergic induced vas constriction)

With regard to other physiologic parameter labetalol has been shown to have a lesser bro choconstrictive effect than propranolol with sim lar degrees of beta blockade (possibly mediated b alpha adrenergic blockade)[5, 15] The effects labetalol on platelet function hemoglobin ox gen dissociation electrophysiologic function an glucose metabolism have not been well elucidate to date

Therapeutic applications and clinical experience

The hemodynamic profile of labetalol sug gested its application in cardiovascular disorde such as hypertension ischemic heart disease an cardiac arrhythmias

Hypertension The major clinical experienc with labetalol to date has been in the treatmen of hypertension β adrenoceptor agents lik propranolol reduce blood pressure mainly b lowering cardiac output[15] (perhaps also through central nervous system effect) but do no primarily or consistently affect peripheral vascu lar resistance[16] β adrenoceptor blockade may b effective in some patients with hypertension bu usually must be combined with other antihyper tensive agents (diuretics vasodilators)[17]

Constriction of the peripheral resistance vessel is mediated through α adrenoceptors Pur alpha blockers (phentolamine) have not foun much clinical application in hypertension becaus of their unpleasant side effects reflex tachycardi and orthostatic hypotension[11] An agent like labe talol combining the properties of efficientl blocking both the alpha adrenoceptors of th resistance vessels and the β adrenoceptors in th heart can be anticipated to lessen blood pressur by decreasing the peripheral resistance and at the same time inhibit the reflex increase of heart rate and cardiac output

Labetalol has been shown to be an effective and safe antihypertensive agent in multiple clinical trials to date[1, 3] Short term intravenous trials with the drug in hypertension (1 to 2 mg/Kg) have shown dramatic reductions in both systolic and diastolic blood pressure (usually within 5 to 20 minutes) during rest while exercise induced rises in systolic and diastolic pressures were considerably attenuated[1, 27, 3] Labetalol is the first beta blocker that intravenously has proven effective in hypertensive crises[31] Although there is a dramatic reduction in blood pressure in the standing position the incidence of dizziness and syncope has been infrequent (probably because labetalol is not as potent an alpha adrenoceptor blocker as phentolamine)

In oral doses of 25 to 3 200 mg/day labetalol has shown to be efficacious both in the short term and long term (up to 3 years) management of hypertension[21, 1] Most patients with mild to moderate hypertension responded to doses of 400 to 800 mg/day[24] Postural hypotension and dizziness were usually seen with doses over 2 000 mg/day[3] Drug tolerance does not develop[3]

In 16 patients resistant to conventional antihypertensive therapy (a multi-drug regimen) oral labetalol was effective by itself in normalizing the blood pressure However high doses of drug (range 1 200 to 8 000 mg/day mean daily dose 3 901 mg) were required with postural hypotension a bothersome side effect necessitating discontinuance of the drug in three subjects

In controlled comparative trials oral labetalol (800 mg/day) proved more efficacious than oral propranolol (320 mg/day) in the management of moderately severe hypertension Group average heart rates were lower in patients treated with propranolol compared with labetalol Labetalol caused a greater fall in blood pressure in the standing position and attenuated the exercise induced rise in blood pressure

In another comparative study oral labetalol (400 mg/day) proved a more efficacious antihypertensive agent than a combination of oxprenolol phentolamine[1] In two comparative intravenous studies in hypertension labetalol was shown to be more effective than propranolol

Labetalol has been shown to be useful in the medical and surgical management of patients with pheochromocytoma and relieved symptoms in a patient experiencing hypertensive crisis after clonidine withdrawal[31] The drug was extremely well tolerated in patients undergoing surgery with halothane anesthesia[3]

Labetalol is an important new addition to the antihypertensive regimen currently available As a single drug it has been therapeutically equated with a propranolol hydralazine combination[1] It can be used in hypertensive crises without causing the secondary tachycardia seen with diazoxide and hydralazine[34] Since it does not decrease cardiac stroke volume[1] it may be a useful drug in hypertensive patients with associated coronary and/or cerebral insufficiency

The major side effects seen in patients treated with labetalol are postural hypotension and dizziness which are usually self limited however some patients cannot tolerate the drug for these reasons[32, 33]

The effects of labetalol on renin angiotensin and aldosterone levels are not well defined although there is some preliminary evidence that elevated renin levels are attenuated[19]

Ischemic heart disease There is very little experience with labetalol in the management of angina pectoris One study showed the drug to be effective in increasing exercise tolerance in patients with angina[3] The mechanism of the therapeutic effect of beta blockers in angina pectoris is the reduction of heart rate and blood pressure increments with exercise[3] Labetalol lowers the heart rate blood pressure product with exercise and should prove to be clinically efficacious The unique alpha blocking effect of labetalol may also provide additional therapeutic benefit Alpha receptors are present in the coronary arteries and a drug which can block adrenergic tone may increase blood flow while myocardial oxygen demands are being reduced A study by Maxwell in dogs showed that intravenous labetalol increases the coronary blood flow in contrast to other beta blockers where the opposite effects on coronary blood flow have been demonstrated Studies are now in progress in our institution comparing labetalol to a propranolol nitrate combination in patients with angina pectoris With coronary spasm now being recognized as a possible cause for angina pectoris and myocardial infarction labetalol with its alpha adrenergic properties might prove to be extremely useful for these indications[0]

Arrhythmias There is very limited clinical experience with labetalol in therapy of cardiac

Table III Adverse reactions and toxicity—collected series (350 patients)

Adverse reactions
1 Postural dizziness (postural hypotension usually seen with high doses (2 000 mg/day)
2 Nasal stuffiness (rare)
3 Fatigue (rare)
4 Nightmares (rare)
5 Bronchospasm (rare)
Toxicity
No clinical toxicity seen to date
1 Occasional antinuclear antibody titre elevation
2 Reversible binding of drug to melanin in uveal tract of eye (no ophthalmologic symptoms)

rhythmias Since labetalol has beta blocking properties identical to propranolol, it should prove efficacious in those clinical settings where propranolol has proven to be effective

Congestive heart failure Labetalol with its alpha adrenergic blocking (vasodilating unloading properties) might prove efficacious in hypertension angina pectoris and arrhythmias with associated mild to moderate congestive heart failure where pure beta adrenoceptor blocking drugs are contraindicated Preliminary hemodynamic studies in hypertensive patients have shown no deterioration in left ventricular function with therapeutic doses of labetalol

Side effects and toxicology (Table III) The most common side effects of labetalol is postural dizziness related to postural hypertension In a collected series of 350 patients this symptom appeared in 3 to 5% of patients during initiation of treatment however it was self limited in most instances When high doses of the drug are used (2 000 mg) this side effect is more commonly seen with frequent patient intolerance

Other side effects which were rarely noted were fatigue nightmares (usually with high doses) nausea bronchospasm and nasal stuffiness

Labetalol binds reversibly to the melanin pigment of the uveal tract of they eye Unlike the drugs chlorpromazine and chloroquine no clinical opthalmic signs have been demonstrated to date However continuous clinical observation is necessary because of the oculomucocutaneus syndrome that has been seen with another beta blocker practolol

Occasional patients have demonstrated positive antinuclear titers but no associated cl[illegible] symptoms have been described

Conclusions

Labetalol is the forerunner of a new group beta adrenoceptor blocking drugs with the pro[perties] of combined alpha and beta adrenocept[or] blockade The drug has been proven useful treatment of hypertension with a low incidence postural hypotension The therapeutic applic[a]tions of this drug in angina pectoris and arrhyt[h]mias might provide another exciting applicatio[n] of sympathetic blocking agents in clinical prac[ti]tice

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Of bloodletting

It is well known that a high hematocrit is associated with high viscosity and that a highly viscous fluid requires more work of the pump to circulate it than does a less viscous fluid Furthermore the flow of highly viscous fluid is reduced even with all else being equal. Nevertheless physicians fail to bleed patients with active coronary disease and myocardial ischemia whose hematocrit is high and whose blood viscosity is increased It has been shown that bloodletting in patients with ischemic heart disease definitely improved the clinical state of these patients when their hematocrit was reduced to average normal levels The technic of bloodletting has been described and the results indicated previously Bloodletting in patients with erythrocytosis or polycythemia can help to improve blood flow to all vital organs, including the heart brain and kidneys.

Could it be that the procedure is rarely used because it appears to be "old fashioned" "antique" and not "modern"? If the concept is good and the clinical results often dramatic, why not use it? Just because "bloodletting" is a procedure of the old days and one that was misused this does not justify not using it today

Some old things are good Antiques are desirable and appreciated and antiquities are even more precious and valuable People by the millions visit the King Tut exhibit—including doctors But the King Tut exhibit is not modern That which is good or useful must be preserved—even bloodletting for definite clinical indications, such as with angina pectoris and other types of ischemic heart disease

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Intermittent claudication—A preventable condition?

Peripheral vascular disease has been less studied than the other clinical manifestations of atherosclerosis. We have recently published the findings of a series of investigations designed to determine the risk factors for intermittent claudication (I C) and to examine in detail the prognostic importance of the different factors in established cases.

A group of unselected I C patients was identified by sending questionnaires, similar to those described by Rose and Blackburn to all men and women aged 45 to 69 years on the lists of two Oxfordshire general practices. The over all response to the postal questionnaire was 90% and further follow up of a random sample of non responders suggested that all symptomatic subjects had replied I C was diagnosed in patients who had a history of leg pain associated with exercise and relieved by rest and whose resting systolic blood pressure ratio (ankle systolic blood pressure measured by a Doppler ultrasonic flowmeter brachial s o h n pressure) was below 0 75 falling to below 0 6 ft r er ise Th age-standardized prevalence among men w ~ and among women it was 1.2% Approximately hal f t mptomatic patients had consulted their doctors because of their symptoms For each patient identified as having I C two controls matched for age and sex, were selected randomly from the alphabetical listings for each general practice All I C. patients and controls underwent detailed clinical examination, a 12 lead electrocardiogram was recorded and various estimations were made on a blood sample taken after a 14 hour overnight fast.

The risk of having I C was about nine times greater among those who smoked more than 15 cigarettes daily than among nonsmokers among those who smoked less than 15 cigarettes daily the relative risk was 6 1 Raised levels of systolic (≥160 mm Hg) or diastolic (≥90 mm. Hg) blood pressure were associated with an approximately threefold increase in the risk of I.C Concentrations of plasma triglyceride uric acid, and fibrinogen were all significantly higher among the patients with I C than among the controls. The presence of more than one factor appeared to be associated with a multiplicative increase in risk. Cholesterol an important risk factor for ischemic heart disease was not associated with as

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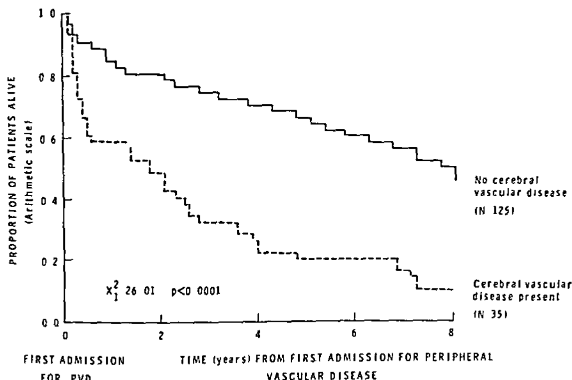


Fig 1 The effect of cerebral vascular disease on the survival of patients admitted to hospital for peripheral vascular disease

increased risk of I C There were more diagnosed persons with diabetes among the I C group (11%) than among the control group (1%) but levels of blood glucose did not differ significantly Myocardial infarction angina and stroke had all occurred appreciably more frequently among the I C patients who also more often had ischemic changes on the E C G

We also had the opportunity of investigating 60 I C patients five years after they had been referred because of their symptoms, to the Radcliffe Infirmary Oxford Similar investigations to those already described had been carried out at the time of referral To investigate which factors might predict an unfavorable outcome we defined an adverse event" as any of the following (1) death (2) amputation (3) onset of I C in a previously asymptomatic leg (4) onset of rest pain in a limb previously free of rest pain (5) myocardial infarction or cerebrovascular accident in a patient with no history or evidence of coronary artery or cerebrovascular disease and (6) operation for deterioration of peripheral vascular disease

Only one patient had never smoked All the rest were cigarette smokers on referral and were strongly urged to discontinue smoking Any beneficial effect of stopping smoking might be expected to take a while to become evident Accordingly considering only those adverse events which occurred *after* the first year from first referral approximately 2% of those who stopped smoking or reduced to fewer than five cigarettes per day experienced an adverse event within the subsequent four years During the same time period around 60% of those who continued to smoke had a similar experience There was no significant difference in the number of cigarettes smoked per day at the time of referral between those who subsequently stopped or smoked less and those who continued smoking nor were there differences in age at onset age at first referral claudication distance or prevalence of other risk factors In this investigation patients who had had a stroke before referral had a particularly bad prognosis when compared with those with no history of cerebrovascular disease

The small numbers of patients in this study necessitated the use of a variety of adverse events as end points in the analysis which could account for our inability to show that ischemic heart disease diabetes hypertension and hyperlipidemia were important prognostic factors To obtain further information on the natural history of I C we used the Oxford Record Linkage Study (ORLS) to identify all 160 patients discharged from hospital after a first admission for peripheral vascular disease in the Oxford region during 1965 66 This information system also provided data on subsequent hospital admissions surgical procedures, and deaths up to the end of 1972 Hospital records were examined for information concerning risk factors and life tables were constructed using death or amputation as end points.

In this study inadequate data concerning smoking were available and evidence of ischemic heart disease cerebrovascular disease and diabetes were the chief factors associated with an adverse outcome An example of one of the life tables is shown in the Fig 1

These 160 patients had a total of 480 hospital admissions

during the follow up period and spent 11 190 days in hospital The average duration of each admission (excluding convalescent admissions) was 18 days twice as long as the average duration of admission to general ho pitals in the ORLS area for all causes during the period The life expectancy of these patients after the age of 60 was about half that of the general population

Thus I C is associated with a significantly reduced life expectancy appreciable morbidity and a considerable drain on Health Service resources the most important findings in these studies concern smoking Smoking emerged as the strongest risk factor for I C thus implying that this common and disabling manifestation of atherosclerosis may be largely preventable The observation that risk factors exert a multiplicative effect may be of great clinical significance since the limination of even one factor may greatly reduce the risk of C Even after the diagnosis of I C it is extremely important at patients be persuaded to stop smoking since this appeared to be the only potentially correctable risk factor with an appreciable effect on prognosis

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Late complications of prosthetic heart valves
A pathologist s viewpoint

Mo t patients who have an artificial heart valve inserted return home and enjoy a prolonged life Their subsequent death is due either to late complications associated with the pro thesis or more frequently to other causes At autopsy such patients show a variety of lesions some develop immediately before death others evolve as the patient or prosthesis age and others result from pre operative investigation or surgical treatment The lesions found related to the prosthesis in the heart or in distal organs may have caused death morbidity or no symptoms Some occur in any patient irrespecti e of the type of prosthesis inserted but others are uniquely associated with particular prostheses because of their structure or design

Late complications common to all heart valve prostheses Thrombus formation at component interfaces or in areas of relative stasis is a major problem Careful prosthesis design and the coating of surfaces with pyrolytic carbon have reduced their frequency on non tissue valves but 30% of early models have thrombi attached to them at necropsy Most are small if they are large or organized the thrombi may stenose the orifice or interfer with occluder movement or seating and cause prosthesis dysfunction Thus anticoagulant therapy is generally used with non tissue valves It an cause morbidity or an occasional late death This and the fact that thrombus formation is less of a problem with tissue valves favors their use However thrombus may thicken or splint a cusp of a tissue valve

Thromboemboli arise most often fr m non ti sue valves especially those in the mitral area Again their frequency has diminished as prosthesis design impr ve M st thromboemboli must be tiny with m ny passing to th brain A major embolus may lodge in any v ss l Th s au ing death are infrequent and are usually foun l in r bi l arteries r much less often in the coronary system

Fatal infectious endocarditis m r ft n aff t an aortic than a mitral prosthesis Staphylo r Strept ci are the usual cause but fungi and organisms not commonly a cause of infectious endocarditis are encountered The infection can pread locally and cause dehiscence and a paraval ular leak (Other small dehiscences unrelated to infection are fou d at the perimeter of a prosthesis in approximately 20% of necropsy cases and may aggravate hemolysis or heart failure) Annular abscesses which occur predominantly in the aortic area, burrow into surrounding tissue forming fistulae or damage the conducting system Healed endocarditis may be found by a pathologist Possibly that developing on porcine xenografts is easier to treat

All prostheses cause hemolysis especially cloth co ered, non tissue valves Renal hemo iderosis is the usual morphological finding but in the rare instance where anemia becomes severe and requires repeated blood transfu ion hemosiderosis may be observed in many organs

Minor disproportion between the prosthesis and the chamber into which it projects usually causes slight endocardial thickening at the site of impingement on the chamber wall Alternatively some obstruction of the left ventricular outflow tract may result Major disproportion where struts are incorporated into the wall with resultant prosthe s dysfunction is rare In general disproportion is more likely with ball valves or the long supporting struts of xenografts

Blood turbulence associated with a prosthesis may damage the lining of a chamber into which it projects and cause thickening The change is more likely to be severe with lateral flow prostheses Its functional significance is not known

Patients with artificial heart valves are prone to sudden death At necropsy a cause may be obvious and be related to the prosthesis However many patients show only severe coronary artery disease Possibly the current practi e of treating valve and coronary artery disease simultaneously may affect the frequency of these deaths

Iatrogenic lesions caused during investigation or surgical treatment These may occur in any patient or may be the

result of a particular procedure used by an individual physician or surgeon. They include foreign body emboli, a variety of vascular injuries, annular separation causing false aneurysm formation, and myocardial injury. Most of these lesions cause little or no symptomatic effect. Myocardial injury leading to focal myocardial fibrosis may be a basis for subsequent heart failure found in a patient without obvious fault in his prosthesis.

Late complications of particular heart valve prostheses. The insertion of a heart valve prosthesis tests to the utmost the durability of its components and the efficacy of its design. Rigorous bench tests may indicate that both are excellent but nature over the years may decide otherwise. Thus some late complications in non tissue valves are the result of a revealed weakness in design or arise from an unfortunate choice of material used in prosthesis manufacture. Again, tissue valves may be affected by poor design and the question of their durability is not settled. Such problems are of necessity evolutionary. When discovered, the prosthesis is either abandoned or its design is improved. The group of patients bearing the affected prosthesis must be monitored carefully to determine if the problem is developing and to establish the best time to replace the prosthesis.

This annotation is not intended to be pessimistic because these complications affect a small number of patients. Nevertheless, complacency about the prostheses that are presently available is not warranted. Present models are better than earlier ones, but this improvement must continue as knowledge widens and technology improves.

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Marathon running and the heart: The South African experience

Current interest in the possible role of marathon running in the prevention of coronary heart disease stems directly from the statement by Bassler in 1972 that "a search of the literature by the American Medical Joggers Association failed to document a single death due to coronary atherosclerosis among marathon finishers." Later he concluded that "when the level of vigorous exercise is raised high enough, the protection appears to be absolute."[2]

Our own interest in the "Bassler hypothesis" arose from a telephonic report, subsequently confirmed by letter, of autopsies in two cases of sudden death in long distance runners. This information formed the basis of our Letter to the Editor. However, further inquiry revealed that the autopsies reported to us had either not been performed, or where completed, written reports and autopsy material were not available. Thus our earlier report was erroneous and in no way disproves Dr. Bassler's contention that autopsy proven coronary atherosclerosis has not been found in a marathon runner.

We have subsequently limited our reports strictly to cases either examined by ourselves, or to cases when autopsy material or angiograms have been examined by several observers in Cape Town. In four of a total of seven cases of sudden death in marathon runners were adequate autopsies done on the heart: one showed hypertrophic cardiomyopathy, another showed a normal heart although the material is still being reviewed, and two showed fatal atherosclerosis. A fifth athlete who died with severe chest pain highly suggestive of acute myocardial infarction had an electrocardiogram compatible with, but not diagnostic of, acute inferior subendocardial ischemia, but no autopsy was done. The interpretation of this ECG has been challenged, but heatstroke can be excluded in the context of the full clinical details as verified from the runner's log book and by his wife.

Five marathon runners who suffered heart attacks have also been studied. In four of these athletes angiography confirmed the presence of myocardial infarction. Two athletes had

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significant arterial disease of two major arteries a third has stenosis of the anterior descending and a fourth of the right coronary artery Angiographically the coronary artery disease in these four marathon runners was indistinguishable from coronary atherosclerosis. In one of these athletes coronary atherosclerosis was subsequently shown at autopsy There fore we conclude that these four athletes had coronary atherosclerosis the development of which was not absolutely prevented by their marathon running although of course its progression may well have been retarded

Three additional facts are of interest First *despite subsequently documented coronary artery disease all these athletes were able successfully to complete numerous marathon races before they suffered myocardial infarction or sudden death* With only one exception all athletes with on fatal heart attacks returned to marathon or longer istance running on their own again t our advice and without edical supervision Despite exertional angina triple vessel ease and a large area of akinetic left ventricle one athlete twice recently completed the 56-mile Comrades Marathon 0½ hours Other reports of successful marathon running in persons with triple vessel disease are available The lesson as first emphasized by Kavanagh and colleagues is that coronary artery disease is not an absolute contraindication to marathon running which, however should ideally be carefully controlled. The corollary however is that the ability to complete a marathon does not guarantee the absence of significant cardiovascular disease

Second *two athletes developed myocardial infarction during marathon racing in the absence of complete coronary artery occlusion at angiography* There is growing interest in the concept of myocardial infarction with normal or near normal coronary arteries and various reports of athletes who developed cardiac problems despite their having normal coronary arteries are available Thus Green and associates have reported a fatal myocardial infarction occurring during a marathon race in an athlete with normal coronary arteries at autopsy while Frick and colleagues report a runner with angiographically normal coronary arteries, ischemic electrocardiographic changes during exercise testing and a demonstrable area of myocardial underperfusion Cantwell has described a veteran marathon runner with angiographically normal coronary arteries who collapsed during exercise and required cardiopulmonary resuscitation A subsequent exercise stress test provoked couplets of ventricular premature beats at a heart rate of 100 beats per minute More recently Cantwell and Fletcher described the sudden death while jogging of a non marathon running physician whose coronary arteries were normal at autopsy Possibly severe exertion could act to precipitate myocardial ischemia in a small minority of marathon runners even in the absence of coronary artery disease Alternatively exercise may induce certain arrhythmias

Thirdly *without exception each athlete had continued training or indeed racing despite mpt ms* Three athletes completed marathon races with mpt ms one of these athletes running more than 20 miles fter the onset of exertional discomfort to complete the 56 mile Comrades Marathon One athlete who died had c ntinu d training for 3 weeks, including a 0-mile run with he t pain which he ascribed to "unfitness The athlete d ed during a marathon race had suffered previou t ack hest pain and remarked that he felt unwell and wi hed t quit during the fatal race [8] One month before his subsequent death during a 1? mile road race another athlete had visited his physician complaining of a lack of energy" Two other athletes continued to train in spite of chest pain.

How do these cases relate to the Bassler hypothesis"? One feature of the "Bassler hypothesis is its flexibility Despite frequent re statement it is not exactly clear what it entail, and immunity to ischemic heart disease to coronary heart disease to fatal myocardial infarction to loafer s heart, and to coronary atherosclerosis have all been proposed. A statement like autopsy proven coronary atherosclerosis as the cause of death has never been found in a marathon runner" is no longer correct in view of our most recent report Further more when reviewed by an independent pathologist," Bassler s own data appear to include one case of sudden death (Case No 16) in a marathon runner with coronary atherosclerosis Current data cannot exclude the possibility that marathon running might increase resistance to sudden death even in those who have coronary atherosclerosis but this conclusion cannot on epidemiological grounds be inferred from Dr Bassler s data Milvy has shown that in a non marathon running cohort of American men matched for age weight, and a similar smoking prevalence to that of the 9,9?8 male Americans who completed marathon races in 19 5 the annual mortality rate from ischemic and related heart disease would be between one or two deaths per annum. Even if marathon running were to provide 100% protection from sudden death due to coronary heart disease the difference between no deaths and the predicted two per annum would be impossible to prove statistically

Dr Bassler s hypothesis can also be stated differently i e "fatal coronary atherosclerosis has never been reported in an active marathon runner therefore all marathon runners are immune to coronary atherosclerosis." Neither parts of the statement are we believe now tenable in view of our own angiographic findings of coronary artery disease in marathon runners the possible presence of coronary atherosclerosis in Dr Bassler s own material, and our own more recent, autopsy studies

Conclusion

Although our autopsy data disprove the Bassler hypothesis " we believe that Dr Bassler has beneficially publicized the role of exercise and life style modifications in the prevention of and rehabil tation from coronary heart disease His hypothesis has also encouraged a more critical look at the pathology of cardiac death and has uncovered the problem of exercise-induced cardiac problems even in persons with normal coronary arteries

On the basis of present admittedly incomplete evidence we believe that marathon running by encouraging a life style associated with low coronary risk probably acts a ainst the development of coronary artery disease but that this protection is not absolute Marathon runners who manifest coronary artery disease may do so because (1) the disease was present before they started running or (2) because they have uncorrected coronary risk factors (like smoking hypertension, or hyperlipidemia) or (3) because marathon running may not effectively prevent coronary artery disease Thus sometimes despite the marathon running and even in the absence of established coronary risk factors coronary atherosclerosis may be found. Furthermore we have shown that marathon running itself may occasionally be associated with sudden

death or acute myocardial infarction due either to underlying coronary artery or other cardiac diseases or sometimes even in the absence of detectable heart disease At present it seems likely that the small group of runners at risk of cardiac catastrophe will probably have warning symptoms whereupon they should stop running and seek out adequate medical attention.

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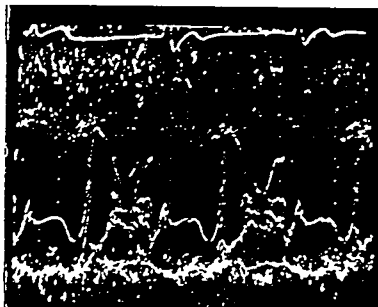


Fig 1 Case of mitral valve prolapse in which echoes can be seen during diastole and with a protodiastolic space mimicking a prolapsing left atrial myxoma.

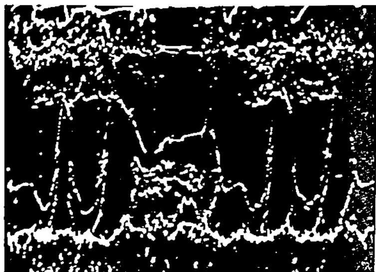


Fig 2 The same case of prolapsed mitral valve as in *Fig 1* in which the diastolic echoes were seen much better after a long pause due to extrasystoles Again there is a protodiastolic space mimicking a pedunculated left atrial myxoma. The angiocardiograms do not indicate the presence of tumors

Pseudo tumor mitral valve prolapse sign

To the Editor:

We have read with interest the article b Drs Liedtke Babb and DeJoseph "Mitral valve echoes in patients with mitral valve prolapse syndrome pub ished in the AMERICAN HEART JOURNAL (97 286 1979 in whi h the describe an unusual echocardiographic finding reporte h ir study in 12 of 83 patients (14.5%) with mitral al e p se ndrome The finding consisted of a pattern of multiple, high intensity parallel echoes behind the anterior mitral leaflet noted throughout diastole which, in character were closely akin to those previously observed in left atrial myxoma or hemody namically significant flail mitral valve leaflet. The authors point out they were able to find only one prior reference to the presence of this phenomena in the literature published in 1976

For historic interest we would like to clarify that we

published this sign of pseudotumor mitral prolapse in 1974 in Spanish in the *Journal of the National Institute of Cardiology* in Mexico City Volume 44 No 6 pages 851-859 November December 1974 Unfortunately this Journal was circulated in Spanish speaking countries and Europe and was not widely circulated in this country

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Reply

To the Editor

We are grateful to Drs. Alvarez and Sasse for calling to our attention their case report which appeared in the *Archives of the Institute of Cardiology of Mexico* In their article they describe two patients with the mitral valve prolapse syndrome one of whom was a 54 year old man with an echocardiographic picture similar to that observed in left intra atrial tumorations The related figures show echo reflections beneath the anterior mitral valve leaflet in diastole Although the echo reflections do not fill the space beneath the anterior leaflet as in our patients, the findings are otherwise akin to those we described and probably reflect a subpopulation of prolapse patients with enough excess leaflet chordal tissue to repetitively curl during left ventricular inflow It is always encouraging when describing a new sign to discover confirmatory evidence from other laboratories and investigators We are indebted to Drs Alvarez and Sasse for providing such information

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Vasospastic initiation of coronary artery thrombosis

To the Editor

The vasospastic initiation of coronary artery thrombosis as so succinctly reviewed by Hellstrom (AM HEART J 97 449 1979) is a welcome addition to our understanding of the etiological mechanisms operative in myocardial infarction Certainly this work is in accord with much of the current work especially that of Maseri and associates[3-5] suggesting once again what Lathem and Osler[2] in 1876 and 1910 predicated if in a less sophisticated fashion

In support and perhaps in extension of this it should not be forgotten that alpha stimulation in the non anesthetized patient profoundly affects not only resistance but likewise conductance vessels Furthermore it should be remembered that when platelets are aggregated by thrombin or in endothelial injury thromboxane A is released which in turn appears to have a profound vasoconstrictor effect and that further more alpha adrenergic receptors have been demonstrated on human platelets

Thus a cascade theory" of myocardial infarction is at least tenable While it should not be invoked as the only cause leading down the final common pathway of myocardial necrosis it certainly might well be worthy of consideration in conceptualizing these etiological mechanisms

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Reply

To the Editor:

Dr. Loewy's comments about the coronary artery paper (AM HEART J 97:449, 1979) are appreciated. Thrombosis is but one part of the puzzle, but elucidating its mechanism should help resolve the major issue of the pathogenesis of infarction.

Dr. Loewy discusses possible mechanisms for *spasm*. It is agreed that the autonomic nervous system probably is involved and spasm secondary *to an inappropriate* autonomic nervous system response was postulated to link infarction with stress. I have *reservations* whether platelets are involved significantly in the initiation of spasm, mainly because of the strong relation of *myocardial ischemia* to infarction and angina. There is supporting evidence for the positions that severe ischemia can cause spasm and that exertion can trigger attacks of spasm.

However, the *injury-spasm* concept probably has paid insufficient attention to platelets. Platelets might play a role operating in conjunction with injury spasm. Platelets aggregate with *experimental partial* coronary occlusion, and atheromatous and stenotic coronary arteries might cause release of vasospastic *substances* from platelets because of intimal roughening or flow abnormalities. A balance between vasospastic *and vasodilative forces* recently was proposed, and any release of vasospastic substances from platelets would *augment spastic forces* secondary to severe ischemia and stress. Also, once infarction is underway, secondary endothelial *damage could* activate platelets and release vasoconstrictors, worsening the necrosis.

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Sleep apnea and Q-T interval prolongation—A particularly lethal combination

To the Editor:

In the April 1979 issue of AMERICAN HEART JOURNAL, Smith, Mason, Bell, and Francisco report a case of an infant *dying at 20 days of age unobserved*, who had had an electrocardiogram taken at one day of age which they report as having a prolonged Q-T interval. They present the electrocardiogram and in reading the record with a magnifying glass, I find that the great majority of complexes show a Q-T interval of .28 sec., rather than .30 sec. Using the venerable Q-T normal values from Ashman and Hull,[1] this value is longer than the average, but within the limits of normal for any age subject for the heart rate of 150. Calculating the QTc, the great majority of beats show a value of .44, which is actually the *mean* QTc for newborns. Values in the literature show a QTc for the first six months of life in normal subjects to extend up to .49.[2] Later, the authors state that "T wave alternation is noted in Leads I, II and V_4." My inspection of those leads reveals a wandering baseline and *no* alternation.

On the basis of an electrocardiogram with a QTc that is average for a newborn and with no physiologic observations whatsoever and an unobserved death of unknown cause, the authors claim that this case is "unique in providing a link between cardiac and respiratory mechanisms of death in a SIDS victim!"

It should be remembered that SIDS is an autopsy diagnosis based on the absence of lethal pathology and can include even homicidal suffocation. The authors' link, then, is between a normal ECG finding and an unexplained death, and reveals nothing about cardiac or respiratory mechanisms.

The authors subsequently assert that they have "demonstrated that about one half of SIDS victims die in respiratory failure and another half die in circulatory failure." This study is based on the temperature of the corpse and arterial PO_2, obtained at an unknown interval after death and with no apparent correction for ambient temperature or resuscitation attempts, etc. The body temperatures ranged from 1? C to 38° C, and the PO_2 in their series ranged from zero to 125 mm Hg. To claim that the distribution of arterial PO_2 for these 2? cases of SIDS can demonstrate cause of death is naive, to put it favorably.

Finally, they claim to be "one of the first to substantiate the mechanism for SIDS as proposed by Schwartz." They do not cite the work of Maron, Clark, Goldstein, and Epstein reported in *Circulation* in 1976, who surveyed 42 families of infants with SIDS, examining for long Q-T.[3] They included in this report an infant with a "near miss" of SIDS with marked prolongation of the Q-T interval. However, Kelly, Shannon, and Liberthson found in a series of 21 such aborted SIDS cases *no* prolongation of QTc compared to the literature or to normal infants in their own hospital.

The uniqueness of this case report is in its exaggeration.

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Reply

To the Editor

Dr Guntheroth is quite correct that some of the Q T intervals are 0 28 sec He is also right that the corrected value of a Q T of this length is within the range that some authorities consider normal

On these issues our reply is that there are Q T intervals of 0 30 sec and this corrected value of 48 sec is considered outside the range as quoted by some authorities

We readily admit one can use authorities that would claim the tracing in this case falls within the range which could be called normal

This is not the purpose of reporting this case In this situation a child was actually tested in the newborn period had a tracing that can be considered abnormal by some authorities and subsequently became a victime of SIDS Because there are a limited number of prior reported cases (none to our knowledge) we believed it should be documented and reported This is not a "near miss"

SIDS is not a disease with a proved etiology or pathogenesis. It is truly a disease of theories Until this disease can be studied and its mechanisms clarified we believe that all *rational theories should be explored To be proved incorrect* on the altar of time and the scientific process is no mistake The only mistake in the world of science is to close one s mind to plausible theories

This case represents a theory with some support To have a simple case report receive this degree of attention is most welcome and we hope that many will read the report with the same interest as Dr Guntheroth

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Book reviews

Electrocardiology—I Edited by M J Gandhi MD A B *Mehta MD and D B Pahlajani MD Published by D B* Pahlajani, 168 B Vikas Wadi, Dr Ambedkar Road Bombay 400 014 India 244 pages

These proceedings reflect the discussions presented at a symposium on electrocardiography conducted in Bombay India during 1975 The papers presented were on selected aspects of electrocardiography (ECG) but they fail to critically review the many galloping studies" made in ECG For example what really are the recent advancements in His bundle recording surface mapping etc? And what are the research advancements? What are the practical clinical advancements? Those who are qualified to critically review these presentations are already well acquainted from the regular journals with these problems in electrocardiology and with the ECG procedures, whereas the practicing physician who is not following the medical literature closely needs to know the clinical significance of these procedures The book contains ideas of the various contributors on selected aspects of ECG This should interest cardiologists and internists who practice a great deal of cardiology Some of the contributions should interest as well those beginning to learn electrocardiography

Echocardiography Interpretation and Diagnosis By J J Kleid and S B Arvan New York 1978 Appleton Century Crofts Inc. 460 pages. Price $36 50

This book on the interpretation of echocardiograms is another addition to many others already available The book reviews in an organized manner the history physics of ultrasound equipment normal tracings and recordings obtained in the common cardiac disease states The book is a good source of review of echocardiography an important addition to clinical diagnosis This is a good book The recordings published are clear and well selected. This reviewer cannot conclude that it is superior to some previous publications on the subject but it is a good and authoritative one It is recommended as a good book on the subject.

Cardiac Catheterization and Angiocardiography By David *Verel and Ronald G Grainger* New York and London 19[illegible] Churchill Livingstone Publishers 238 pages Price $[illegible]9.50

This third edition on Cardiac Catheterization and Angiocardiography is forewarded by Sir John McMichael The history of angiocardiography outlined briefly by him is interesting and clearly written Those who employ these procedures should own and study this book It is well organized brief and clearly written The illustrations are well selected and clear The authors fail to discuss sufficiently the errors and the corrections necessary to record fairly accurately the time course of intraluminal pressures of the circulation and the heart with the catheter tip in the lumen under investigation and the sensing transducer on the outside of the patient or animal at the other end of the catheter The time course curves of pressure are rarely if ever accurate as used in catheterization laboratories today The error or accuracy of cardiac output in catheterization laboratories needs careful and accurate discussion Nevertheless the thoughtful and meticulous physician who has carefully and extensively reviewed and learned the literature on hemodynamic principles and phenomena and principles of hydraulics before entering the catheterization laboratory will understand the problems of cardiac catheterization This is a good book intended for clinical service rather than fundamental research.

British Medical Bulletin–Thrombosis Volume 34 Number 2 London May 1978 Published by the British Council.

Each issue of the *British Medical Bulletin* is an exciting important and worth owning The publications are regularly excellent This is true of this issue on Thrombosis The selected papers on thrombosis review the problem extremely well and thoroughly All clinicians should be interested in owning this May 1978 issue The present interest in oral contraceptives deep vein thrombosis and platelet suppressive therapy renders this issue of the *Bulletin* of greater value to practicing physicians. This is an excellent and important publication

Books received

Noninvasive Techniques in Cardiology for the Nurse and Technician By A Benchimol New York 1978 John Wiley & Sons, Inc 316 pages Price $16 95

Progress in Hemostasis and Thrombosis vol 4 Edited by Theodore H Spaet New York 1978 Grune & Stratton Inc., 410 pages Price $34 50

Comprehensive Immunology Edited by Robert A Good and Stacey B Day New York 1978 Plenum Publishing Corp 763 pages Price $45 00

Thrombosis—Animal and Clinical Models Edited by H James Day Basil A Molony Edward E Nishizawa and Ronald H Rynbrandt New York 1978 Plenum Publishing Corp 337 pages Price $35 00

The Thrombotic Process in Atherogenesis Edited by A Bleakley Chandler Karl Eurenius Gardner C McMillan Curtis B Nelson Colin J Schwartz, and Stanford Wessler New York 1978 Plenum Publishing Corp 546 pages Price $4 50

1978 Year Book of Cardiology Edited by Proctor Harvey M D Walter M Kirkendall M D., John W Kirklin M D., Alexander S Nadas M D Oglesby Paul M D and Edmund H Sonnenblick M D Chicago 1978 Year Book Medical Publishers, Inc 439 pages

American Board of Internal Medicine Recertification Examination

The third Recertification Examination in Internal Medicine of the American Board of Internal Medicine will be administered at test centers throughout the United States on Saturday October 2, 1980 Any certified internist who was certified or recertified in internal medicine prior to 1975 is eligible to take this examination

The purpose of the Recertification Examination in Internal Medicine is to provide the practicing certified internist an opportunity to demonstrate his or her current clinical knowledge and problem solving abilities that relate to the provision of excellent care in internal medicine The Board adminsitered Recertification Examinations in 1974 and 1977 and 6400 internists have already been recertified

The Recertification examination will be a comprehensive 1-day proctored examination It will consist of a half day session of multiple choice questions and a half-day of sequential latent image patient management problems All of the questions will relate to clinical information in general internal medicine with an emphasis on recent advances in internal medicine Much of the examination will reflect the content of the syllabus and the questions in the American College of Physicians Medical Knowledge Self Assessment Program (MKSAP V)

The fee for the examination is $175 applications for the examination will be accepted November 1 1979 through June 1 1980 For application forms write to American Board of Internal Medicine 3624 Market Street Philadelphia PA 19104

Angiography and Vascular Disease 1980

A course entitled Angiography and Vascular Disease 1980 will be conducted on January 20 through 25 1980 at the Hilton Hotel San Diego California The course is designed for clinicians surgeons and radiologists interested in vascular disease An interdisciplinary approach to vascular disease will be presented integrating basic reviews and recent developments Emphasis is on interaction between angiography and other diagnostic modalities and recent clinical and therapeutic advances New developments in interventional techniques will be explored The course carries 24 hours of Category I CME credit or 24 hours of AAFP credit (elective) For further information contact Edith S Bookstein Program Assistant Office of Continuing Education M 017 School of Medicine University of California San Diego San Diego Calif 92093 Telephone (714) 4 > 3 04

Workshop on Stress Management for Physicians and Psychologists

A workshop on stress management will be offered in Chicago on December 2 through 5 1979 It will be co-sponsored by the University of Chicago Center for Continuing Education and by the Institute for the Study of Human Knowledge Topics will include Identifying Type A behavior Biofeedback and relaxation Remaining healthy in the encounter with stress and Stress inoculation Full accreditation through the University of Chicago and various medical associations will be available For further information, contact Claude M Weil Associate Director Center for Continuing Education University of Chicago 1307 E 60th St Chicago Ill 60637 Telephone (312) 753-3186

Special Nuclear Cardiology Course

William Beaumont Hospital, Royal Oak Michigan, is offering a three month course in Nuclear Cardiology which will enable the participant to fulfill the Nuclear Regulatory Commission s requirements for a byproduct license limited to Nuclear Cardiology Two hundred hours of Category I approved credit are available The course starting date will be arranged by mutual agreement tuition for the course is $4 000 For further information contact John E Freitas, M D., Nuclear Medicine Dept William Beaumont Hospital, 3601 W 13 Mile Road Royal Oak Mich 48072

Cardiology Preceptorship

A Cardiology Preceptorship program is being offered by the San Francisco General Hospital and the University of California School of Medicine The primary emphasis of the program will be to involve the participant in the activities of the Coronary Care Unit The preceptor will be encouraged to develop his or her skills in critical care and to participate in work rounds and teaching rounds Current cardiology methods, non invasive and invasive are available for study The program is approved for Category I credit by Extended Programs in Medical Education of the University of California School of Medicine in San Francisco For further information write Elliot Rapaport M D Department of Cardiology San Francisco General Hospital 5G 1 San Francisco Calif 94110

Acknowledgment to reviewers

The Editors wish to express their thanks and appreciation to the members of the Editorial Board and to the following who have aided in the review of manuscripts during the past year

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ıtorial

ɟorphins—the first three years

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· three years have passed since the firs rts on the presence of a previously unknown p of endogenous substances the endorphins ared. These compounds were identified on ..ass that they should be morphinomimetic presumably be involved in the endogenous ..l of pain. Subsequent work has indicated the physiologic role of these peptides may be more extensive. For instance they are found number of different tissues and not only in e cell.

emically speaking, it seems clear that there two different endorphin systems. In the en ..alin system there are two pentapeptides ..onine-enkephalin and leucine-enkephalin, ..ctively which seem to co-exist in the same The active compound in the other system is ..mabl β-endorphin, a peptide with 31 amino and with the N terminal pentapeptide ..ence identical to the structure of methio- ..enkephalin. Despite the chemical similarity there is evidence that the two systems have a ..ent biosynthetic origin. β-endorphin appears formed from a macromolecule which also is precursor of β-lipotropin and ACTH.

..bodies have been prepared against these ..ides and immunohistochemical techniques been instrumental in the mapping of endor distribution. The enkephalins are present in areas of the CNS and highly concentrated to limbic system and to pain pathways. They also been found in the intramural ganglia of gastrointestinal tract and sympathetic gan particularly of the alimentary canal. The ..phalins are also present in peripheral nerves

..m as ... has been ... enkephalin ... Enkephalins are quite unstable in ... enzymes ... has recently been demonstrated. ... it seems probable that the enkephalins may have a neuro... role in the central and peripheral nervous systems.

Enkephalins are also found in non-neuronal tissues such as paracrine cells of the gastrointestinal tract, the adrenal medulla, and the salivary gland. If enkephalin is released into the blood, it is rapidly degraded and it may be questioned whether such enkephalin could reach distant target such as the CNS in significant amounts.

The distribution of β-endorphin is markedly different from that of the enkephalins. In the CNS β-endorphin is present in a diffuse projection from the hypothalamus to the thalamic centra. There is no overlap with any enkephalin pathway. Outside the CNS β-endorphin is only found in the anterior pituitary where it occurs in the same cells as ACTH. At least in rodents, stimuli which release ACTH will also release β-endorphin and in equimolar amounts. The presence of β-endorphin in human blood is subject to some controversy and it has been questioned whether the pituitary production gives significant levels in the human being. β-endorphin is much more stable both in brain where it may produce analgesia for several hours, and in blood where the half life is of the order of 10 minutes. It is therefore probable that β endorphin may reach receptors far from the area of synthesis. β endorphin would therefore be a modulator or a hormone in the CNS and in the periphery.

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β-endorphin and a neurotransmitter like or short range acting hormonal system enkephalins These two systems may be ementary the former giving a tonic and l activity the latter a localized amplifica The intrinsic activity in these systems may lustrated by the fact that certain electrical ulation techniques clinically used for pain f seem to act via endorphins (being naloxone " and being accompanied by increases in release) These techniques frequently adequate pain relief for patients with pain The mechanisms for activating release is an important goal for future

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Clinical communications

Re evaluation of a possible high incidence of hypertension in hypothyroid patients

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A number of endocrine disorders have been considered to cause high blood pressure in man Among them hypothyroidism has been listed as one of the causes of high blood pressure[1] but the data were inconclusive to support this concept For instance Thompson and associates had reported in 1931 that incidence of high blood pressure was extraordinarily high in patients with severe hypothyroidism Unfortunately however exact evaluation of thyroid function was not possible at that time because of lack of accurate diagnostic techniques Furthermore they failed to compare the data with age related increase of blood pressure found in normal subjects In a textbook of hypertension published recently Strong and colleagues stated that as many as 50% of untreated hypothyroid patients had blood pressure of 150/90 mm Hg or more Although the author and journal were not indicated this discussion might possibly be based on the data of Thompson and co workers Recently Barnes[4] insisted that hypertension was prevalent in hypothyroid patients without showing any exact data

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Because of these uncertainties we have re evaluated a possible high incidence of hypertension in slight moderate and severe hypothyroid patients

Materials and methods

Evaluation of hypothyroidism and euthyroidism was based on the measurement of serum thyroxine (T_4) triiodothyronine (T_3) and thyroid stimulating hormone (TSH) before and after intramuscular injection of 500 μg thyrotropin releasing hormone (TRH)[5] Female subjects with blood pressure above 160 mm Hg systolic and/or 95 mm Hg diastolic at each of three weekly visits were considered to have hypertension The reading of blood pressure was made with the subjects comfortably placed in the recumbent position and the cuff was applied to the arm at the level of the heart The pressures at which the first rhythmic sound appeared and the sound disappeared were taken as the systolic and diastolic blood pressures

All hypothyroid patients have circulating thyroid autoantibodies (microsomal and thyroglobulin) indicating that dishormonogenesis was due to Hashimoto s thyroiditis Eighty female patients were divided into three groups depending on serum T_4 concentrations (slight hypothyroidism $T_4 > 4.0$ μg/100 ml moderate hypothyroidism $4.0 < T_4 < 2.0$ μg/100 ml severe hypothyroidism $T_4 < 2.0$ μg/100 ml) All the patients were treated with T_4 The initial dose of T_4 was 10

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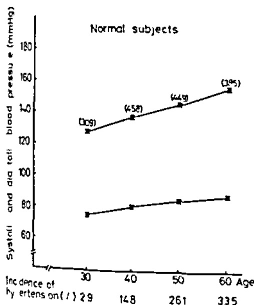


Fig 1 Mean systolic *(above)* and diastolic *(below)* blood pressures and incidence of hypertension in 1601 normal subjects. *Circles and bars* indicate mean ± SE

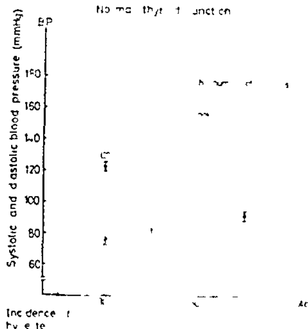


Fig 2 M pressures an subjects *Cir*

to 25 μg/day and was increased at 10 to 14 day intervals by 10 to 25 μg/day to avoid possible cardiac complications until serum TSH concentrations before and after TRH were normal. Effects of T_4 treatment on blood pressure and laboratory data were re evaluated only in severe hypothyroid patients. Blood pressure 3 to 4 months after normalization of serum TSH concentration was considered as the blood pressure after treatment. To indicate electrical activity and size of the heart $Sv_1 + Rv_5$ and cardio/thorax (C/T) ratio were used.

Serum T T, and TSH concentrations were measured by radioimmunoassay using commercially available kits. For statistical analysis Student's t test was used. A p value less than 0.05 was considered statistically significant.

Results

Blood pressure in people living in Matsumoto city and Kijimadaira village. In our first step systolic and diastolic blood pressures were studied in 1601 female subjects living in Matsumoto city and Kijimadaira village. All the subjects appeared euthyroid as evidenced by normal physical examinations but no thyroid function tests were performed to confirm this assumption in those subjects. As shown in Fig 1 systolic and diastolic blo d r re e ively with age. In t e t n each decade was progres ve t e age.

In the second tep t ar l tolic blood pressures were studied in te t le s bjects living in Matsumoto city and Kijimadaira village. Serum T T, and TSH concentrations were completely normal in these subjects (T 8.3 ± 0.1 μg/100 ml T, 129.0 ± 0.8 ng/100 ml basal TSH 3.4 ± 0.1 TSH after TRH 21.1 ± 1.0 μU/ml). As shown in Fig 2 systolic and diastolic blood pressures increased progressively with age the pattern being exactly comparable to that found in the first step. Incidence of hypertension was also increased progressively with age although the incidence at the fifth decade was unexpectedly high.

Blood pressure in hypothyroid patients. In the first step both systolic and diastolic blood pressures were measured in 38 female patients with slight hypothyroidism. In this group T and T, were slightly less (T 6.1 ± 0.1 μg/100 ml T, 115.1 ± 5.4 ng/100 ml) and compensatory increase of TSH was apparent as evidenced by an increase of TSH before and after administration of TRH (basal TSH 20.0 ± 2.2 TSH after TRH 118.2 ± 6.7 μU/ml). No typical signs of hypothyroidism were found in any of the patients studied.

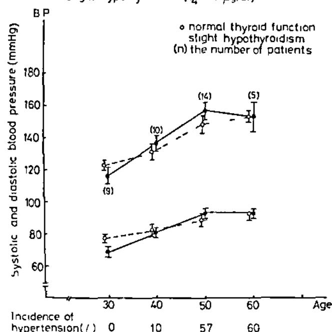


Fig 3 Mean systolic *(above)* and diastolic *(below)* blood pressures and incidence of hypertension in slightly hypothyroid patients For comparison blood pressure in known euthyroid subjects *(dotted line)* was indicated *Circles* and *vertical lines* indicate mean ± SE

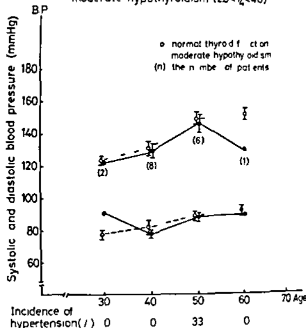


Fig 4 Mean systolic *(above)* and diastolic *(below)* blood pressures and incidence of hypertension in moderate hypothyroid patients For comparison blood pressure in known euthyroid subjects *(dotted line)* was indicated *Circles* and *vertical lines* indicate mean ± SE

Serum cholesterol (208 ± 5 mg /100 ml) the pattern of the electrocardiogram (ECG) and C/T were normal in all patients Blood pressure in this group was compared with that of euthyroid subjects As shown in Fig 3 systolic and diastolic blood pressures increased progressively with age as was shown in Fig 2 Incidence of hypertension was high in the fifth and sixth decades

In the second step systolic and diastolic blood pressures were measured in 17 female patients with moderate hypothyroidism In this group serum T_4 and T_3 concentrations were below normal (T_4 3 1 ± 0 1 μg/100 ml T_3 38 0 ± 2 0 ng /100 ml) Basal and TRH stimulated TSH levels increased significantly (basal TSH 85 8 ± 10 7 TSH after TRH 253 0 ± 5 5 μU/ml) indicating that compensatory increase of TSH could not overcome the dishormonogenesis due to Hashimoto s thyroiditis Slight clinical symptoms such as dry skin and constipation were found in 10 of 17 patients In accordance with this abnormality of ECG pattern (low flat or negative T wave) and a slight increase of serum cholesterol (238 ± 10 mg /100 ml) and C/T (54 ± 2%) were found in eight of 17 patients Although the number of patients studied were limited systolic and diastolic blood pressures increased progressively with age, as is seen in Fig 4 However incidence of hypertension was less as compared to the euthyroid group

In the final step systolic and diastolic blood pressures were measured in 26 female patients with severe hypothyroidism In this group serum T_4 and T_3 were markedly reduced (T_4 1 2 ± 0 1 μg/100 ml T_3 52 2 ± 6 3 ng /100 ml) and as a result serum TSH before and after TRH increased markedly (basal TSH 163 6 ± 6 4 TSH after TRH 303 1 ± 6 3 μU/ml) Typical symptoms of hypothyroidism were found in all patients Changes of ECG pattern (low flat or negative T wave) and an increase of serum cholesterol and C/T were found in all patients (Table I) As compared to euthyroid subjects systolic and diastolic blood pressures in the fifth and sixth decades were lower (Fig 5) The incidence of hypertension in the fifth and sixth decades was lower than that shown in Fig 2 Three to 4 months after normalization of serum TSH C/T Sv_1 + Rv_5 serum cholesterol and blood pressure were re evaluated in patients in the fifth and sixth decades (Table I) Serum cholesterol and C/T decreased significantly after T_4 administra

[illegible] whereas $S_{V_1} + R_{V_5}$ increased significantly after treatment. Systolic and diastolic blood pressures elevated after T_4 treatment but the increase was of questionable significance.

Discussion

In order to re-evaluate a possible incidence of hypertension in hypothyroid patients, we first [illegible] systolic and diastolic blood pressures in a large scale of normal subjects who were living in the same area as the hypothyroid patients. An increase of systolic and diastolic blood pressure in 1601 subjects was similar to those found in a large scale of subjects in Japan. The next step was to measure systolic and diastolic blood pressures in normal subjects who were euthyroid as judged by serum T[illegible] T[illegible] and TSH concentrations. The data were comparable to those found in 1 601 [illegible], although the incidence of hypertension [illegible] high in the fifth decade for an unknown [illegible].

[illegible] establishing this aspect, we studied the [illegible] of hypertension in hypothyroid pa[illegible]. If thyroid hormone deficiency does accelerate [illegible] development of hypertension, the incidence of hypertension should be prevalent in hypothyroid [illegible] depending on the severity of hypothy[illegible]. Thus we divided hypothyroid patients [illegible] three groups depending on serum T[illegible] concentrations. In patients with slight hypothyroidism, [illegible] increase of mean systolic and diastolic blood [illegible] with age was similar to those found in [illegible] thyroid subjects. As compared to euthyroid [illegible], however, the incidence of hypertension [illegible] high in the sixth decade. Since no clinical [illegible] of hypothyroidism were found and [illegible] laboratory findings on C/T, ECG and [illegible] were normal, it is difficult to interpret [illegible] incidence in terms of thyroid hormone defi[illegible]. Rather this might be due to the small [illegible] of patients studied. Age related increase [illegible] [illegible] and diastolic blood pressures in moder[illegible] hypothyroid patients was comparable to that [illegible] in euthyroid subjects, but the incidence of hypertension was somewhat lower. Quite inter[illegible] [illegible] systolic and diastolic blood pressures in [illegible] fifth and sixth decades of severe hypothyroid [illegible] are lower than those seen in euthyroid [illegible]. Also the incidence of hypertension is [illegible]. Thus our data do not support the generally [illegible] hypothesis that hypertension is prevalent in hypothyroid patients. Rather blood pressure and

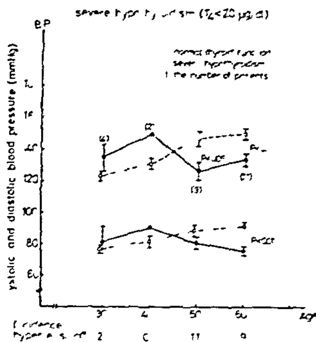


Fig 5 Mean [illegible] (above) and diastolic (below) blood pressures [illegible] (hypertension in severe hypothyroid patients. For [illegible] blood pressure in known euthyroid subjects [illegible] was indicated. Circles and vertical lines indicate mean [illegible] SE

Table I Increase in blood pressure after administration of T[illegible] in severe hypothyroid patients

Parameter	Before treatment	After treatment	p value
[illegible] of subjects	1[illegible]	13	
Systolic blood pressure (mm Hg)	130 ± [illegible]	140 ± 9	0.0[illegible] < p < 0.1
Diastolic blood pressure (mm Hg)	[illegible]3 ± 4	81 ± 3	0.0[illegible] < p < 0.1
Serum T[illegible] (μg/100 mL)	1.0 ± 0.2	8.2 ± 0.2	p < 0.001
Serum T[illegible] (ng/100 mL)	[illegible] ± 1[illegible]	100 ± 2[illegible]	p < 0.001
ECG S_V + R_V (mm)	22 ± 2	30 ± 2	p < 0.01
C/T (%)	[illegible] ± 2	[illegible]3 ± 0.[illegible]	p < 0.05
Serum cholesterol (mg/100 mL)	290 ± 19	2[illegible] ± 16	p < 0.05

± mean [illegible] SE; patients in the fifth and sixth decades were analyzed.

the incidence of hypertension are low in severe hypothyroid patients.

At present it is not possible to give a complete explanation for the difference between the findings of Thompson and associates and our observations. However a number of clinical and experimental findings may be considered to explain our

findings In severe hypothyroid patients heart rate was lowered cardiac output was reduced,[7, 11] and peripheral blood flow diminished Furthermore blood volume in severe hypothyroid patients was reduced[7, 12] Since blood pressure is determined by cardiac output, circulating plasma volume and peripheral resistance it is less likely that the hypothyroid state accelerates the incidence of hypertension Experimental studies indicated that the hypothyroid state reduced blood pressure in spontaneously hypertensive rats but that the administration of thyroid hormone raised blood pressure to the pre thyroidectomy level[13, 5] In accordance with these clinical and experimental findings we found a slight increase of systolic and diastolic blood pressures after the shift of Av_1 + Rv and C/T toward normal produced by T_4 treatment

Summary

In an attempt to re evaluate a possible high incidence of hypertension in hypothyroid patients blood pressure was measured in 38 slightly hypothyroid patients in 17 moderate hypothyroid patients and in 26 severe hypothyroid patients The data were then compared with the findings in 73 known euthyroid subjects and in 1 601 possibly euthyroid subjects

Blood pressure and incidence of hypertension increased progressively with age in known euthyroid subjects and in possibly euthyroid subjects Similarly blood pressure increased progressively with age in slight and moderate hypothyroid patients but the incidence of hypertension was high in the sixth decade in slightly hypothyroid patients for some unknown reason In contrast blood pressure and the incidence of hypertension were low in the fifth and sixth decades in severe hypothyroid patients This low blood pressure was elevated slightly when Sv_1 + Rv and C/T were shifted toward normal by T treatment for 3 to 4 months

It is suggested that the hypothyroid state does not accelerate the development of hypertension

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Rate of progression of severity of valvular aortic stenosis in the adult

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Valvular aortic stenosis in the adult patient can occur as a result of rheumatic heart disease congenital malformation of the aortic valve or fibrosis and calcification of a bicuspid or tricuspid aortic valve[1] Obstruction occurs as a result of incomplete commissure formation as with the unicuspid and acommissural or domed" aortic valve fusion of the commissures with rheumatic heart disease or gradual fibrosis and calcification with age as seen with bicuspid aortic valve the -called calcific aortic stenosis

In time obstruction progresses because of rther fusion of commissures as in rheumatic art disease or more commonly because of ntinued fibrosis and calcification seen in all rms of aortic stenosis How rapidly the stenosis an progress is unknown The purpose of this tudy is to obtain an estimate of the rate at which ortic valve obstruction can increase in the adult atient by retrospectively studying patients with alvular aortic stenosis who were serially cathe terized without an intervening operative proce dure and to determine whether progression of the severity of aortic stenosis could be predicted by history physical examination chest roentgeno gram or electrocardiogram

Methods

This study involved three hospitals Walter Reed Army Medical Center in Washington D C Fitzsimons Army Medical Center in Denver Colorado and the Veterans Administration Hospital San Francisco California Clinical catheterization and surgical files were searched for patients with documented aortic stenosis over age 20 at first catheterization who had serial catheterizations without intervening aortic valve surgery All patients had at least the peak systolic gradient (PSG) across the aortic valve measured on both occasions to be included in the study Because mean aortic gradient systolic ejection period and aortic valve area were rarely calcu lated when the gradient was low we chose PSG as a measure of the severity of the aortic stenosis

Thirty-eight patients were found The patients were classified according to etiology on the basis of the following criteria rheumatic heart disease if there was concomitant mitral stenosis and/or insufficiency congenital heart disease if the patient had isolated aortic stenosis with a history of a murmur from childhood and calcific aortic stenosis if the patient had isolated aortic stenosis discovered after age 30 with calcification of the valve on fluoroscopy or chest x ray

Historical information with particular empha sis on chest pain syncope and signs and symp toms of heart failure was tabulated Details of physical examination with emphasis on severity of aortic steno is and presence and severity of

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Table I Aortic stenosis—progression hemodynamics

Patient number	Sex	Etiology	Cath	Age at cath (years)	Interval between cath (months)	LV Systolic (mm Hg)	LVEDP (mm Hg)
1	F	RHD	First	33	37	150	10
			Second	36		160	8
2	M	–	First	34	120	113	
			Second	44		176	14
3	M	CAS	First	35	72	–	–
			Second	41		190	21
4	M	RHD	First	46	33	160	10
			Second	49		180	22
5	M	CAS	First	49	13	136	10
			Second	50		166	18
6	M	CAS	First	37	35	184	12
			Second	40		235	9
7	M	CAS	First	40	87	120	–
			Second	47		180	20
8	M	CAS	First	43	57	138	3
			Second	48		185	[illegible]
9	M	CAS	First	63	24	140	10
			Second	65		200	14
10	M	CAS	First	35	32	144	16
			Second	37		160	10
11	M	CHD	First	45	46	155	5
			Second	49		180	12
12	M	RHD	First	61	44	146	14
			Second	65		140	16
13	M	CAS	First	55	25	189	16
			Second	58		215	23
14	M	CAS	First	48	41	142	20
			Second	51		200	34
15	M	RHD	First	55	54	90	5
			Second	60		128	
16	M	CAS	First	38	42	190	20
			Second	41		188	23
Mean ± 1 S D			First	44.8 ± 9.7	47.6 ± 26.6	146.5 ± 27.6	
			Second	48.8 ± 9.2		179.5 ± 27.3	

Total intervals = 16

Abbreviations Cath = catheterization LV = left ventricular LVEDP = left ventricular end-diastolic pressure AS = aortic systolic pressure AD = aortic diastolic pressure PSG = peak systolic gradient M = male F = female RHD = rheumatic heart disease CAS = calcific aortic stenosis CHD = congenital heart disease MS = mitral stenosis CA N = coronary arteriography was normal MI = mitral insufficiency CA LAD = coronary arteriography revealed significant left anterior descending coronary lesion S D = standard deviation

Grouped by change in PSG from first to second catheterization PSG of 40 mm. Hg separates low from high A = low to low B = low-to-high, C = high to-high.

aortic insufficiency chest roentgenogram reports and electrocardiogram (ECG) recorded at the time of each catheterization were evaluated when available

The patients were arbitrarily divided into a progressive group and a nonprogressive group defining the progressive group as those with an increase in PSG by 30 or more between the two catheterizations Nine patients were eliminated because of either intervening infective endocarditis or aortic insufficiency of 2+ or more on a scale of 1 to 4+ by aortogram [5] This latter group of patients were excluded because aortic insufficiency increases the systolic flow across the aortic valve and therefore increases the PSG Therefore PSG can no longer serve as an index of

AS (mm. Hg)	AD (mm Hg)	PSG (mm Hg)	Cardiac output (L /min.)	Slope (mm Hg/ month)	Group	Comments
119	63	31	7.2	+0.92	B	MS
95	58	65	–			
104	69	9	–	+0.34	B	CA N
126	70	50	6 6			
–	–	40	–	+0 69	C	
100	52	90	7 4			
120	62	40	–	+1 06	C	CA N MS and MI
105	65	75	4 4			
108	55	28	–	+2 15	B	
110	75	56	–			
147	72	37	–	+2.37	B	
115	80	120	–			
90	–	30	–	+0 80	B	CA N
80	50	100	5 7			
90	76	48	–	+0.56	C	
105	60	80	3 6			
140	80	0	5.3	+3 75	B	CA N
110	75	90	6.5			
108	64	36	–	+0.94	B	CA N
95	60	65	–			
135	75	20	5 0	+0 74	B	CA N
126	74	54	5.3			
138	65	8	5.2	+0.39	A	CA LAD Lesion MS and MI
115	50	25	4.5			
146	78	43	5.8	+1.28	C	CA N
140	65	75	10 4			
125	80	17	7.2	+1 78	B	CA N
110	60	90	–			
82	50	8	2.9	+0.30	A	Severe mitral insufficiency
104	47	24	3.3			
1 0	95	20	5 6	+1.31	B	CA N
113	78	75	5.5			
121.5 ± 24.8	70.3 ± 11 6	25 9 ± 14 6	5 53 ± 1.37	+1.21		
109 9 ± 14 4	65 1 ± 10 5	70.9 ± 25.9	5 75 ± 2 00			

aortic valve area in this group of patients This left 16 progressive and 13 nonprogressive patients There were two patients in the nonprogressive group who had more than two studies thereby allowing the inclusion of two separate intervals for each of these patients All results in the 29 patients were based on the analysis of these 31 intervals

Since the definition of progression as a change in gradient of 50% or greater makes progression dependent on the magnitude of the initial gradient it was possible for a patient with a low gradient on both studies to be classified as having progressed Since symptomatology and electrocardiographic changes depend on the magnitude of the gradient the patients were divided in a second way according to whether the gradient was low or high at the time of each study with the dividing line between a low and a high gradient arbitrarily chosen at 40 mm Hg Using this method of classification there are three possible subgroupings of the interval data

Group A (low to low)—where the gradient started low and remained low

Table III Characteristics of patient groups*

Characteristic	*Non progression*	*Progression*
Number of intervals	15 (13 patients)	16 (16 patients)
Sex	3 female/10 male	1 female/15 male
Etiology	RHD 2	RHD 4
	CAS 6	CAS 10
	CHD 5	CHD 1
	Unknown 0	Unknown 1
Age (years)		
Initial (mean ± 1 SD)	45.9 ± 6.2	44.8 ± 9 7
Follow up (mean ± 1 SD)	49 1 ± 6 1	48.8 ± 9.2
Follow up		
Months (mean ± 1 SD)	39.3 ± 30 1	47 6 ± 26 6
Range (months)	1 week 116	13 120

Abbreviations RHD = rheumatic heart disease CAS = calcific a... stenosis CHD = congenital heart disease

*No statistically significant differences occurred between progress... and nonprogressive groups or between initial and follow up data

Fig 1 shows the PSG plotted against the tim... between studies in the progressive group Note that the mean PSG of the progressive group rises from 25.9 ± 14 6 mm Hg to 70.9 ± 25.9 mm Hg with a mean follow up interval of 47 6 months The slope or average rate of rise of the PSG was 1.21 mm Hg/month It can be seen that most of the patients had a low gradient (< 40 mm Hg) at first catheterization and a high gradient at follow up (> 40 mm Hg) The most rapid change in gradient was from 0 to 90 mm Hg in 24 months Because the division into progressive and nonprogressive groups was arbitrary there were some patients in whom the PSG rose slowly over a long time thus meeting criteria for progression Had these patients been catheterized earlier the PSG might not have increased by our 50% criterion and these patients therefore would have been in the nonprogressive group Also the lower the initial gradient the smaller the rise necessary for the criterion for progression to be met

Fig 2 shows the PSG plotted against time between studies in the nonprogressive group It is apparent that there are really two groups of patients with seven having an initial gradient above 40 mm Hg and remaining high and the remaining eight having an initial gradient below 40 mm Hg and staying low The arbitrary nature of the division into progressive and nonprogressive groups is also evident here with some of the patients having a slope which might have increased the gradient significantly had the duration between the studies been longer In one patient the gradient remained the same for ten years

Fig 3 plots the mean left ventricular systolic pressure the aortic systolic and diastolic pressures and the cardiac output in the ...essive and nonprogressive ... llow ... the ... the ... oth ... ere ... In ... ac ... no

... change in ... would not have a change in sy...oms had a lesser chance of being restudied even though some of these may have progressed Perhaps for this reason exertional syncope faintness and any symptom which could be construed as due to heart failure such as fatigue shortness of breath paroxysmal nocturnal dyspnea or pulmonary edema were all similar in the three groups This was also true of any changes occurring in the chest roentgenograms

There was a significantly higher incidence of

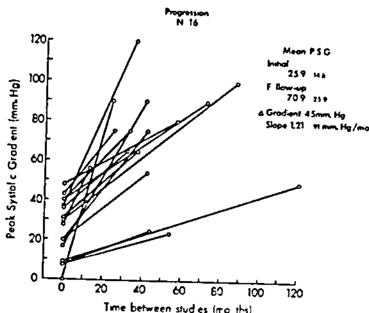


Fig 1 Peak systolic gradient (*PSG*) versus time between studies in the progressive group The first study is placed at time 0

Table IV Summary of systolic pressures and peak systolic gradient

Variable	*Nonprogression*		*Progression*	
	Initial	*Follow Up*	*Initial*	*Follow Up*
LV systolic pressure (mm. Hg)	169.3 ± 36 4	163 3 ± 34.3	146.5 ± 27 6	179.5 ± 27.3
Aortic systolic pressure (mm Hg)	126 0 ± 22.8	117 7 ± 20 3	121.5 ± 24 8	109 9 ± 14 4
Gradient (mm. Hg)	43.3 ± 22 7	45 7 ± 22 1	25.9 ± 14 6	70.9 ± 25.9

Abbreviations LV = left ventricle
*Only statistically significant differences between initial and follow-up data are indicated
$p < 0.002$

typical angina in Group C compared with Group A Thirteen patients had coronary arteriography Eleven had normal coronary arteries and eight of these had angina pectoris at some point in their course Two patients had significant coronary artery disease (> 50% reduction in coronary diameter in at least one major coronary vessel) and only one of these patients was known to have angina pectoris

Of the findings on physical examination that were recorded there were 16 instances where it was specifically stated that no thrill was palpated In nine of these instances the patient had a low gradient and in seven a high gradient Of 22 instances when a thrill was observed seven had low gradients and 15 had high gradients Using the PSG at the second study as one variable a thrill on physical examination at the time of the second catheterization had an r value of 0 73 and this was significant at the P < 0 001 level by Pearson product moment analysis

The ECG was definitely helpful Electrocardiograms were grouped as follows no abnormalities (normal) isolated ST T wave changes high voltage compatible with left ventricular hypertrophy (LVH) by the criteria of Sokolow and Lyon [1] LVH by both voltage and ST T wave changes

Table V lists the ECG in the three groups at the time of the initial and follow up study At the initial study there were five patients with LVH by voltage and ST T wave changes Three had high gradients and the two with low gradients had severe mitral insufficiency At the time of follow up there were eleven with LVH by voltage and ST T wave changes two with mitral insufficiency

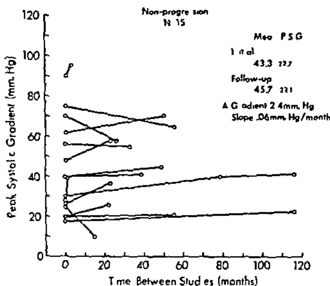


Fig 2 Peak systolic gradient (PSG) versus time between tudies in the nonprogressive group The first study is placed at time 0

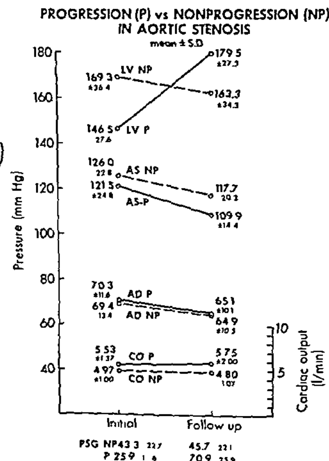


Fig 3 Left ventricular (LV) aortic systolic (AS) and aortic diastolic (AD) pressure and cardiac output (CO) at initial and follow up catheterization The onl ignificant difference between the two studies is the LV s stolic pres ure in the progressive (P) group S D = s tan dard deviation NP = nonprogressive PSG = peak s t li gr dient

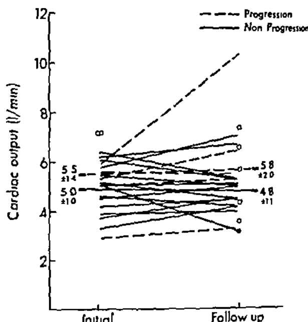


Fig 4 Cardiac output at initial and follow up catheteriza tion o = single individual values

and low gradients and nine with high gradients In Group B there were four with normal ECG s and low initial gradients three of whom devel oped LVH by voltage and ST T wave changes on follow up one remained normal Half the ECGs in Group B changed from the first to the second study In Group C there was one patient with a normal ECG who remained normal with an initial gradient of 40 mm Hg and a follow up gradient of 45 mm Hg four years later Of the remaining seven patients five had developed LVH by voltage and ST T wave changes by the second study

Fig 5 shows the relation of the PSG and the left ventricular systolic pressure to the ECG without regard to any arbitrary grouping The only signif icant differences were in patients with LVH by voltage and ST T wave changes where the left ventricular pressure and PSG were significantly higher than those in patients with normal ECGs or other ECG changes

Discussion

Although the rate of progression of valvular aortic stenosis in adults is unknown there have been several studies reported of serial catheteriza tions without operative intervention in children with congenital valvular aortic stenosis suggest ing rapid progression In 1971 Friedman and colleagues[5] reported seven of nine children with valvular aortic stenosis with measured PSG s

Table V. ECG grouped by change in gradient from initial to follow-up study

Group	Number with both ECGs	ECG findings	Initial (number patients)	Follow-up (number patients)	ECG changed/unchanged (number patients)
A (low-to-low)	5	Normal	0	0	
		ST-T waves	2	2	
		Voltage	1	1	0/5
		Voltage and ST-T waves	2	2*	
B (low-to-high)	8	Normal	4	1	
		ST-T waves	2	2	
		Voltage	2	1	4/4
		Voltage and ST-T waves	0	4	
C (high-to-high)	8	Normal	1	1	
		ST-T waves	3	2	
		Voltage	1	0	2/6
		Voltage and ST-T waves	3	5	

Abbreviations: ECGs = electrocardiograms.
*Both had severe mitral insufficiency.

that rose from 28 mm Hg to 62 mm Hg in a mean follow-up period of six years. The average rate of increase was 0.4 mm Hg/month. Cohen and co-workers reported a prospective study of 15 children (average age 8.5 years at first study) recatheterized after a mean interval of 6.6 years. The PSG during the first study ranged from 5 to 45 (mean 26) mm Hg. At the second study the PSG was 15 to 81 (mean 40) mm Hg. Severe obstruction, defined as a gradient of greater than 50 mm Hg with normal cardiac output or a calculated aortic valve area of less than 0.7 cm²/M² body surface area, developed in six of 15 (40%) patients.

Mody and Mody reported 22 children from 4 months to 13 years of age (mean 4.7 years) with valvular aortic stenosis. They classified the patients into three groups: mild aortic stenosis with PSG less than 50 mm Hg, moderate aortic stenosis with PSG of 50 to 100 mm Hg, and severe aortic stenosis with PSG greater than 100 mm Hg. The mean time between follow-up catheterizations was 6.7 years. At the first study there were 13 patients with mild aortic stenosis and nine with moderate aortic stenosis. At the second catheterization there were only eight remaining with mild aortic stenosis, nine were moderate, and five had severe aortic stenosis. In each of these studies there was poor correlation of PSGs with symptoms, physical examination, chest roentgenogram, and ECG.

A factor complicating interpretation of changes in severity of aortic stenosis in children is the increase in cardiac output and stroke volume which occurs with growth. Without any change in the valve area, the PSG will increase as the patient grows and stroke volume increases. No such explanation is possible for the increased PSG seen in adults with valular aortic stenosis. It is known that if any change in cardiac output occurs with age, the change tends to be a decrease. In this study, where this informatio

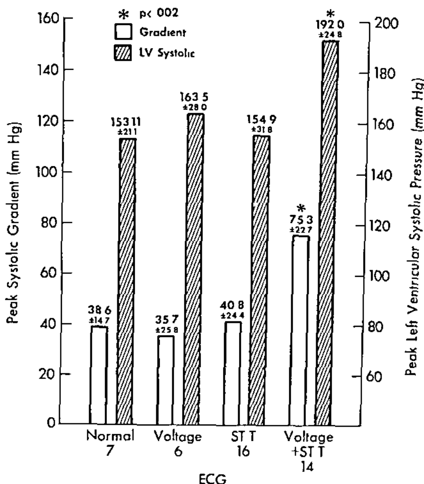


Fig 5 Left ventricular (*LV*) systolic pressure and peak systolic gradient versus the electrocardiogram (*ECG*) classified as normal voltage (voltage for LV hypertrophy) *ST T* (ST T wave changes only) and voltage and ST T wave changes

was available the cardiac output did not change in the interval between the two catheteriza tions

In assuming that the increase in PSG in the face of a constant cardiac output represents an increase in obstruction of the aortic valve the other variable that of the systolic ejection period must be considered because the rise in the gradient might be explained by a shortening of the systolic ejection period In this study it was not possible to obtain data on the systolic ejec tion period because in most instances where the gradient was low it was not recorded However at a given heart rate if the systolic ejection period changes in aortic stenosis it prolongs rather than shortens [10] Consequently because cardiac output remained constant and because the systolic ejec tion period would have remained constant or increased it is probable that the increase in the PSG represents a true decrease in the effective aortic valve area—i e an increase in obstruction probably related to increasing fibrosis and calcifi cation of the valve leaflets [1]

We can make no statement concerning the length of time it takes for progression of aortic stenosis from its inception nor can we say anything about the incidence of progression of aortic stenosis because this was not studied and cannot be studied in a retrospective study The change in PSG with time depends on the mecha nism of obstruction and whether it is a contin uous process or proceeds sporadically It is not known what precise course the change in PSG takes or even if it takes the same course in all cases

By the Gorlin equation [1] the aortic valve area is inversely related to the square root of the gradient As progression of the stenosis occurs at some point a critical effective aortic valve area is reached and there is a rapid almost linear rise in

PSG. Eventually the left ventricle is not able to maintain stroke volume in the face of increasing obstruction and the stroke volume and cardiac output decrease. An increase in systolic ejection period tends to dampen the increase in PSG and as a result the PSG could remain stable despite increased obstruction. Alternatively, there might be no further change in a severely stenosed valve. As the left ventricle fails the cardiac output falls and the gradient decreases. In this study we did not see any patients in this advanced phase.

We have tried to answer the question of how rapidly the PSG can increase by reorganizing the data by slope. If all intervals with PSG increase of 0.45 mm Hg or more/month, irrespective of initial and final gradients, are grouped together there are 18 such intervals. The rate of progression of these intervals is 1.31 mm Hg/month with rates as high as 3.7 mm Hg/month. This may represent the rate at which the PSG can progress in the adult patient with aortic stenosis. It certainly does not imply that all patients or even most patients with aortic stenosis will progress at this rate. In this study, we have patients followed for ten years with only a minimal increase in gradient. All that can be concluded from this study is that when progression occurs, it can be at a rate averaging 1.3 mm Hg/month and as fast as 3 to 4 mm Hg/month.

This is a retrospective study which is biased toward including patients having or developing symptoms. In many cases, a second catheterization was performed because the patient developed new symptoms suggesting progression. For this reason it is not surprising that with the exception of the development of typical angina pectoris, other symptoms did not correlate with the presence of a high gradient. This was also to be expected because all symptoms can be either nonspecific or caused by diseases other than severe aortic stenosis (i.e., congestive heart failure due to severe aortic or mitral insufficiency or hypertension or angina pectoris due to coronary artery disease). Certainly, the development of congestive heart failure or the onset of exertional syncope in a patient known to have mild aortic stenosis still suggests strongly the progression of obstruction and the development of severe aortic stenosis. In this retrospective study, these symptoms did not correlate with the presence of a high gradient.

In this study, the presence of a thrill was often correlated with the severity of the PSG. There were too few observations to decide whether or not the development of a thrill might predict progression. Clinically, Braunwald and associates reported that the absence of a thrill in a patient with an aortic stenosis murmur without a decreased cardiac output and with a normal chest wall configuration was rarely associated with a significant gradient.

The ECG was helpful in predicting the presence of a high PSG if there was LVH by voltage and ST-T wave changes. Voltage or ST-T wave changes alone did not correlate with the presence of a high gradient. In this study, there were only two patients with a low gradient who had LVH by voltage and ST-T wave changes. Both had another explanation for LVH, mitral insufficiency. On the other hand, two patients had normal ECG's with high gradients, so that the presence of a normal ECG did not rule out a high gradient. Occasionally, a normal ECG has been reported in the face of severe aortic stenosis.

Clinical implications

The rate of increase of PSG in adults is similar to that recorded in children with congenital valvular aortic stenosis. The rapid rate of increase in PSG indicates the necessity for careful and frequent follow-up of all patients with mild to moderate aortic stenosis. Although in this retrospective study, only the development of angina pectoris correlated with a change to high PSG, any patient developing symptoms of congestive heart failure or exertional syncope not otherwise explained should be suspected of having developed severe aortic stenosis and should be restudied.

Also, as indicated by this study, any patient developing LVH by voltage and ST-T wave changes should be suspected of having a high gradient and severe aortic valve stenosis.

Summary

In a retrospective study, 29 patients at least 20 years of age with known aortic stenosis are reported who had the peak systolic gradient (PSG) measured on at least two occasions without an intervening surgical procedure or episode of endocarditis. In these 29 patients, there were 31 intervals available for evaluation with a mean follow-up time of 43.5 months (1 week to 120 months). In 16 of the 31 intervals the PSG

increased by 50% or more and in 15 it did not In the group where the PSG increased the average rate of increase was 1 3 mm Hg/month with the most rapid gradient increase at 3 8 mm Hg/month. Progression to high gradient was correlated with the development of angina pectoris or left ventricular hypertrophy by voltage and ST T wave changes In this study, other symptoms were not helpful in predicting an increase in severity It is still recommended however that any patient with aortic stenosis and the development of symptoms of congestive heart failure or exertional syncope should be suspected of having progressed to severe aortic stenosis and should be restudied

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Clinical study on the right-sided Austin Flint murmur using intracardiac phonocardiography

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Intracardiac phonocardiography introduced by Yamakawa and associates in 1953[1] was a breakthrough in the realm of clinical phonocardiography Since the advent of this method it has served as a useful tool for differential diagnosis thus contributing to the analysis of the origin of cardiac murmurs and sounds in the cardiovascular system

Generally conventional external phonocardiography is non invasive and simple but may not always correctly reflect the acoustic events occurring in the cardiac chambers or great vessels Intracardiac phonocardiography on the other hand can localize the origin of cardiac murmurs in a wide variety of cardiovascular diseases and may detect small vibrations inaudible at the chest surface

However little has been reported regarding the right sided Austin Flint murmur in pulmonary regurgitation using intracardiac phonocardiography The purpose of the present study is to discuss the presystolic accentuation of the right ventricular diastolic murmur resulting from relative tricuspid stenosis in pulmonic regurgitation and to comment on the mechanism of its genesis from the hemodynamic standpoint

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Materials and methods

Right heart catheterization was performed on 14 patients with pulmonic regurgitation using intracardiac phonocardiography Their ages ranged from 3 to 53 years The cardiac diagnosis was confirmed by heart catheterization and angiocardiography as shown in Table I Of the 14 patients the diagnosis of nine was eventually verified by surgical intervention

A double lumen phonocatheter manufactured by American Electric Laboratories with barium titanate on the tip or Millar s microtip phonocatheter was introduced into the left axillary vein and advanced to the pulmonary artery via the superior vena cava right atrium and right ventricle All procedures of heart catheterization were performed in the sedated and postabsorptive state after informed consent w s obtained In the majority of cases a simultaneous recording of intracardiac and external phonocardiograms was made in conjunction with an intracardiac pressure tracing with a polygraph (Fukuda denshi EMR 100R or MCM 8000) and a photographic recorder (Sanei sokki 100A) Paper speed was 100 mm /sec in the majority of cases Intracardiac murmurs were usually investigated in the main pulmonary artery right ventricle and right atrium In six cases the left side of the heart was also explored with a phonocatheter

Results

In this study we obtained a pulmonic regurgitant murmur in the outflow tract of the right

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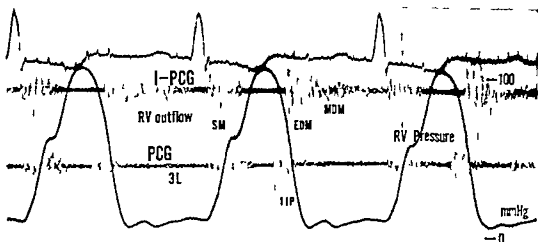


Fig 1 A simultaneous recording of intracardiac phonocardiogram with external phonocardiogram with pressure tracing in a 39 year-old female with atrial septal defect associated with pulmonary hypertension (A. W.) A pulmonic regurgitant murmur is noted in the right ventricular outflow tract The early diastolic murmur is crescendo-decrescendo in configuration beginning from the pulmonic component of the second heart sound and is followed by a mid-diastolic murmur However no presystolic accentuation is noted. Abbreviations *RV* = right ventricle *I PCG* = intracardiac phonocardiogram *PCG* = external phonocardiogram *SM* = systolic murmur· *EDM* = early diastolic murmur· *MDM* = mid-diastolic murmur· *3L* = the third left intercostal space *IIP* = the pulmonary component of the second heart sound.

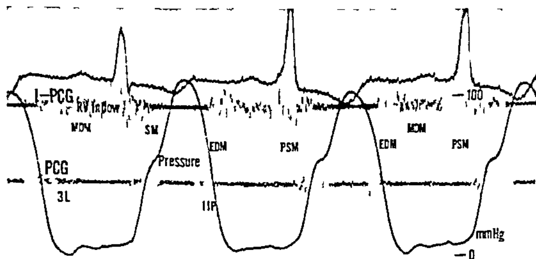


Fig 2 Right sided Austin Flint murmur in the right ventricular inflow tract in the same patient as in *Fig 1* Note a loud presystolic murmur following a mid-diastolic murmur These murmurs are thought to occur due to relative tricuspid stenosis and are regarded as a right sided Austin Flint murmur whereas an early diastolic murmur is thought to derive from pulmonic regurgitation. Abbreviations *RV* = right ventricle *I PCG* = intracardiac phonocardiogram *PCG* = external phonocardiogram *EDM* = early diastolic murmur· *PSM* = presystolic murmur· *MDM* = mid-diastolic murmur *SM* = systolic murmur· *3L* = the third left intercostal space IIP = the pulmonary component of the second heart sound

ventricle of all patients Of the 14 cases seven showed presystolic and mid diastolic murmurs in the inflow tract of the right ventricle which were occasionally transmitted to the right ventricular outflow tract Moreover inspiration augmented the loudness of these murmurs in four cases. These findings are compatible with those of a right sided Austin Flint murmur due to relative tricuspid stenosis

As shown in Table I 10 out of the 14 patients

Table I Findings at catheterization and the incidence of the right sided Austin Flint murmur

No	Patient initials	Age	Sex	Associated heart disease	RV pressure S/ED (mm Hg)	RV pressure (mean) (mm Hg)	Main PA pressure S/ED (mm Hg)	Main PA pressure (mean) (mm Hg)	Right sided Austin Flint murmur
1	Y M	53	m	VSD + PH	[illegible]5/8	([illegible])	60/5	(20)	(–)
2	K M	15	f	VSD + PH	1[illegible]3/10	([illegible]0)	117/6[illegible]	(80)	(+)
3	H K	10	f	VSD + PH + PLSVC	[illegible]	(24)	73/[illegible]	(50)	(+)
4	K T	3	f	VSD + PH	[illegible]8	([illegible])	63/36	(40)	(+)
5	Y T	21	f	ASD	[illegible]/8	(16)	3[illegible]/10	(17)	(–)
6	A W	39	f	ASD + PH	108/10	(3[illegible])	110/38	(60)	(+)
[illegible]	M M	1[illegible]	f	ASD	8[illegible]	(5)	26/8	(16)	(–)
8	S F	19	f	PLSVC	[illegible]0	(6)	[illegible]0/8	(7)	(–)
9	K O	25	f	Single atrium + PH	[illegible]0/0	(30)	90/[illegible]8	(5[illegible])	(+)
10	S I	46	f	MS + PH	60[illegible]	([illegible]8)	60/35	(34)	(+)
11	A S	3	f	MSR + AR + TR + PH	8[illegible]	([illegible]5)	78/35	(55)	(–)
12	M I	19	f	MR	[illegible]	(1[illegible])	24/6	(14)	(–)
13	I H	32	f	Pul branch stenosis + PH	63/11	([illegible]8)	60/5	([illegible]9)	(–)
14	Y I	39	m	PH	10[illegible]/16	(40)	10[illegible]/30	(55)	(+)

Of the 14 patients with pulmonary regurgitation seven showed presystolic and mid diastolic murmurs in the right ventricular inflow tract Ten out of the 14 cases had pulmonary hypertension and the seven patients with right sided Austin Flint murmur showed pulmonary hypertension whereas no presystolic accentuation of the right ventricular diastolic murmur was noted in four patients with normal pulmonary artery pressure

Abbreviations VSD = ventricular septal defect PH = pulmonary hypertension PLSVC = persistent left superior vena cava ASD = atrial septal defect MS = mitral stenosis MSR = mitral stenosis with regurgitation AR = aortic regurgitation Pul = pulmonary S = systolic ED = end diastolic f = female m = male (+) or (–) = presence or absence of right sided Austin Flint murmur in the inflow tract of the right ventricle

had pulmonary hypertension Moreover seven cases with right sided Austin Flint murmur all had pulmonary hypertension whereas the remaining three patients indicated no presystolic murmur in the inflow tract of the right ventricle Thus pulmonary hypertension is thought to be closely related to the production of a right sided Austin Flint murmur

Fig 1 shows a pulmonic regurgitant murmur in the outflow tract of the right ventricle in a patient with atrial septal defect associated with pulmonary hypertension (A W) The early diastolic murmur is crescendo-decrescendo in configuration and is followed by the mid diastolic murmur

Fig 2 shows a right sided Austin Flint murmur in the same case as in Fig 1 Note the extremely loud presystolic murmur in the inflow tract of the right ventricle with a mid diastolic murmur These murmurs are thought to be caused by relative tricuspid stenosis and are regarded as a right sided Austin Flint murmur In contrast an early diastolic murmur is derived from pulmonic regurgitation and is thought to be transmitted from the outflow of the right ventricle

Analogous to the left sided Austin Flint murmur an atrial systole is not considered indispensable for the production of the right sided murmur As shown in Fig 3 a right sided Austin Flint murmur was recorded in a patient with atrial fibrillation resulting from mitral stenosis (S I) In the inflow tract of the right ventricle mid diastolic and presystolic murmurs were recorded when withdrawing the phonocatheter from the outflow to the inflow tract of the right ventricle

The transmission of the right sided Austin Flint murmur to the outflow tract of the right ventricle was noted in three cases Fig 4 shows a presystolic murmur in the outflow tract of the right ventricle in a patient with primary pulmonary hypertension It is thought to be transmitted from the inflow tract (Y I)

In contrast to the functional pulmonic regurgitant murmur an organic pulmonic regurgitant murmur is shown in Fig 5 This intracardiac PCG was taken from a patient with associated ventricular septal defect and pulmonary hypertension (Y M) The diagnosis was confirmed by cardiac surgery The early diastolic murmur is short in duration and has a crescendo-decrescendo configuration However there was no presystolic accentuation of the diastolic murmur in the inflow tract of the right ventricle

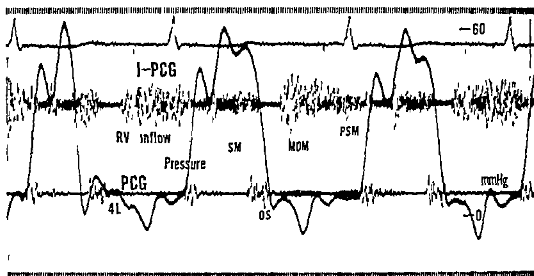


Fig 3 Another example of the right sided Austin Flint murmur in a 46 year old female with atrial fibrillation resulting from mitral stenosis and pulmonary hypertension (S I) A presystolic murmur following a mid diastolic murmur is depicted It is suggested that a right sided Austin Flint murmur occurs even in the absence of atrial systole *OS* = opening snap *4L* = the fourth left intercostal space Other abbreviations are the same as in *Fig 2*

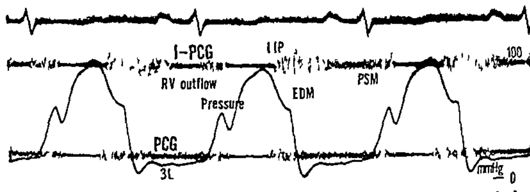


Fig 4 Transmission of right sided Austin Flint murmur to the outflow tract of the right ventricle in a 39 year old male patient with primary pulmonary hypertension (Y I) Note a presystolic murmur in the outflow tract of the right ventricle It is thought to be transmitted from the inflow tract The external phonocardiogram also shows an accentuation of the diastolic murmur Abbreviations are the same as in *Fig 2*

Discussion

Our observations indicated that presystolic accentuation of the right ventricular diastolic murmur was derived from relative tricuspid stenosis in cases with pulmonic regurgitation associated with pulmonary hypertension

Since its advent intracardiac phonocardiography has frequently been used to detect and demonstrate the murmur of organic or functional pulmonic incompetence with pulmonary hypertension either acquired or congenital [3] A major advantage of this method is that it can detect the turbulence due to pulmonic regurgitation from beneath the pulmonic valve without making artificial eddies across the valve in contrast to angiocardiography Injection of contrast dye material into the pulmonary artery may distort the normal closure of the pulmonic valve A pulmonic regurgitant murmur is readily differentiated from that in aortic regurgitation by intra

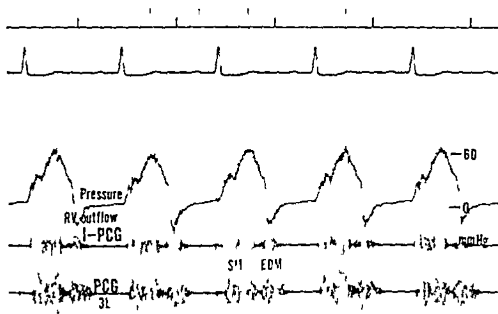


Fig 5 Organic pulmonic regurgitant murmur in a 53 year old male patient with associated ventricular septal defect and pulmonary hypertension (Y M) There are holosystolic and early diastolic murmurs in the outflow tract of the right ventricle In this case however no mid-diastolic murmur nor presystolic murmur was recognized in the inflow tract Abbreviations are the same as in *Fig 1*

cardiac phonocardiography even when other findings are equivocal or not confirmatory

In organic pulmonary regurgitation the murmur is typically low in pitch and crescendo-decrescendo in configuration Its onset in early or mid-diastole is separated from aortic valve closure by a brief silent period Short in duration and ending well before the next first heart sound the murmur is usually heard at the third and fourth left intercostal space adjacent to the sternum Consistent maximal localization of the diastolic murmur to the right ventricular outflow tract leaves no doubt that the murmur arises at the pulmonic valve as a result of regurgitation

The concept of relative or functional pulmonic incompetence due to pulmonary hypertension and dilatation of the valve ring has been entertained Many of the acoustic events associated with functional pulmonary valve incompetence are related to the elevated pulmonary artery pressure and subsequent right ventricular hypertrophy and dilation of the main pulmonary artery Functional pulmonic regurgitation shows a high pitched blowing decrescendo murmur immediately or following the pulmonic component of the second heart sound and it extends through variable lengths of diastole [2]

However it should be noted that little has been reported regarding presystolic accentuation in the right ventricular diastolic murmur This led us to undertake the present study

In our series the pulmonic regurgitant murmur was maximally recorded in the outflow tract of the right ventricle and was occasionally transmitted to the main pulmonary artery It was also usually diminished in the inflow tract of the right ventricle Moreover the presystolic accentuation was noted on withdrawal of the phonocatheter from the outflow to the inflow tract of the right ventricle As a result the right ventricular diastolic murmurs were divided into three patterns in timing that is early mid diastolic and presystolic murmurs

The early blowing diastolic murmur was decrescendo in configuration following the pulmonic component of the second heart sound and it is thought to derive from pulmonary regurgitation In contrast the mid diastolic and presystolic murmurs are attributed to relative tricuspid stenosis These findings are compatible with

of a right sided Austin Flint murmur In addition inspiration increased the loudness of the diastolic murmur in four patients

In a case of atrial septal defect with pulmonary regurgitation associated with pulmonary hyper tension, the presystolic murmur was extremely loud in the right ventricular inflow tract (A W) In unassociated atrial septal defect, an atrio systolic murmur due to relative tricuspid stenosis is usually noted in the right ventricular inflow tract [13] When combined with pulmonary regurgitation atrial septal defect may aggravate the relative tricuspid stenosis and may augment the loudness of the presystolic murmur

Historically speaking MacCallum[3] described a mid diastolic murmur that sometimes had presystolic accentuation and was associated with pulmonary hypertension Wyckoff and associates also observed the apical diastolic murmur unassociated with valvular heart disease in cases of right ventricular hypertrophy Moreover McKusick[5] reported that a right sided Austin Flint murmur occurred in three cases with pulmonary regurgitant murmur associated with pulmonary hypertension

With the aid of intracardiac phonocardiography Green and associates have recently reported a right sided Austin Flint murmur in an autopsied case with Eisenmenger s syndrome and pulmonary insufficiency and they also noted a tricuspid fluttering in the echocardiogram analogous to the left sided Austin Flint murmur in aortic insufficiency

Supporting Austin Flint s original proposal[1] are the findings of Fortuin and Craige [15] namely that the diastolic rumbling murmur occurs as the result of functional mitral stenosis resulting from the effects of an aortic leak on mitral valve movements The principal refinements provided by modern echocardiography are to show that the valve is not held stationary in a semi closed position but is moving swiftly toward a closed position in mid or late diastole while antegrade flow is occurring across it The resultant turbulence leads to the audible vibrations constituting the Flint murmur

Similarly the right sided Austin Flint murmur may result from forward flow across the tricuspid valve at a time when the valve is coming to a close or semi closed position And it is quite probable that the dynamics of right ventricular pressure and flow in diastole play an important role in its genesis Thus the volume of the regurgitant flow as well as the rate of rise of right ventricular pressure in diastole may be the important contributing factors In addition the right sided Austin Flint murmur may not necessitate the atrial contraction similar to the left sided murmur In a case of mitral stenosis with atrial fibrillation (S I), there was a mid disastolic and presystolic murmur in the right ventricular inflow tract It may be attributed to forward flow across a closing tricuspid orifice [16]

Although invasive intracardiac phonocardiography is thought useful for detecting the right sided Austin Flint murmur due to relative tricuspid stenosis as well as the pulmonic regurgitant murmur

Summary

Right heart catheterization was carried out on 14 patients with pulmonic regurgitation using intracardiac phonocardiography All the patients showed pulmonic regurgitant murmur in the right ventricular outflow tract

In addition seven out of the 14 patients showed mid diastolic and presystolic murmurs maximally in the inflow tract of the right ventricle Furthermore inspiration increased the loudness of these diastolic murmurs in four patients These findings were compatible with those of right sided Austin Flint murmur due to functional tricuspid stenosis in pulmonic incompetence

Ten out of the 14 patients had pulmonary hypertension and all the subjects with a right sided Austin Flint murmur showed elevated pulmonary arterial pressure Thus pulmonic regurgitation with pulmonary hypertension is thought to be closely related to the right sided Austin Flint murmur and the turbulence resulting from antegrade flow across a closing tricuspid valve may be responsible for the genesis of this murmur

We would like to thank Mr Yoshihisa Kitamura for his technical assistance We are also grateful to Mr John M Shields for his correction of this manu cript

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Quinidine therapy in hospitalized patients with ventricular arrhythmias

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Although quinidine was introduced for the treatment of cardiac arrhythmias in 1918 its pharmacokinetic properties in patients with cardiac disease are still not fully established Many early studies used non specific analytical methods which measure not only quinidine but its metabolites In addition many reports in the literature deal primarily with normal volunteers and/or present only single dose data [1 7]

We have recently developed a high performance liquid chromatography (HPLC) assay that is specific for quinidine It excludes the known metabolites of quinidine and separates quinidine from dihydroquinidine a contaminant which may be present in marketed quinidine dosage forms in an amount of up to 20% In the present study we used this new assay to assess steady state kinetics in hospitalized patients receiving oral quinidine sulfate for the treatment of ventricular arrhythmias

Methods

Patient selection All patients studied were hospitalized in the Coronary Care Unit of the Baltimore Veterans Administration Hospital and were receiving oral quinidine sulfate for the treatment of ventricular arrhythmias The dose of quinidine was determined by the physicians responsible for the clinical care of the patient Written informed consent was obtained before the patient was entered into the study

The study group consisted of 19 male patients ranging in age from 45 to 81 years with a mean age of 61 years Twelve patients had atherosclerotic heart disease three had cardiomyopathy and four had miscellaneous forms of heart disease Five patients were in New York Heart Association Functional Class 3 or 4 Thirteen patients were being treated with digoxin five with lidocaine and one with propranolol

Study protocol All patients received a complete history and physical examination on admission to the Coronary Care Unit The following laboratory tests were performed within 48 hours of obtaining blood and urine samples for measurement of quinidine levels complete blood count urinalysis SMA 18 12 lead electrocardiogram and chest x ray An echocardiogram was obtained in 16 of the 19 patients

In each case quinidine sulfate had been administered in an oral maintenance dose of 200 300 or 400 mg every 6 hours for at least 5 half lives before steady state samples were obtained Four patients receiving 200 mg every 6 hours were studied both during the first dosing interval and at steady state Venous blood samples of 3 to 5 ml were obtained immediately before and at 1 2 3 4 5 and 5¾ hours after a dose of quinidine The

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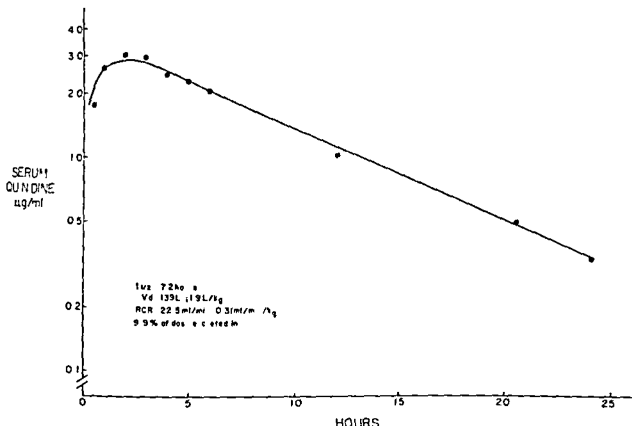


Fig 1 Serum quinidine levels for 24 hours following discontinuation of quinidine in a patient receiving 200 mg every 6 hours *The solid line* shows the computer estimated serum concentrations and *the circles* denote the actual serum levels as assayed in the laboratory Selected pharmacokinetic data are as shown t½ = half life Vd = volume of distribution RCR = renal clearance rate

amples were refrigerated prior to centrifugation The plasma was then frozen for later quinidine determination Urine was collected over the 6 hour dosing interval and after measurement of the total volume a 15 to 25 ml aliquot was saved and frozen for later determination of quinidine and creatinine concentrations Urine pH was measured during most dosing intervals and was acidic in all cases in which it was measured

Echocardiographic measurements The echocardiographic left ventricular internal dimensions in diastole ($LVID_D$) and in systole ($LVID_S$) were determined as described by Feigenbaum and associates[11] The echocardiographic ejection fraction (EF) was calculated by the formula

$$EF = \frac{(LVID_D) - (LVID_S)}{(LVID_D)}$$

Quinidine assay Quinidine levels were determined by a high performance liquid chromatography assay method recently developed by one of us (W G C) This assay excludes known quinidine metabolites and separates quinidine from dihydroquinidine a contaminant which may be present in marketed quinidine dosage forms in an amount of up to 20% In this assay a sample of serum plasma urine or saliva is extracted with benzene evaporated to dryness and reconstituted with methanol containing an internal standard An aliquot is then injected into the high performance liquid chromatograph The sensitivity of the assay is 0 05 $\mu g/ml$ with a coefficient of variation of 3 8%

Protein binding of quinidine was determined in patient serum samples by equilibrium dialysis using 1 ml serum and 1 ml pH 7 4 buffer Both serum and buffer were assayed for quinidine by the HPLC assay method after 18 hours of incubation at 37 C

Data analysis Pharmacokinetic data were fit using the SAAM 27 program of Berman and Weiss and the one compartment open model

Table I Summary of quinidine pharmacokinetics in patients* at three dosage levels

Dose	Peak concentrations (μg/ml)	Peak time (hr)	K (hr)	$t_{1/2}$ (hr)	Vd (L/Kg)	TBC (ml/min/Kg)	RCR (ml/min/Kg)	NRCR (ml/min/kg)
200 mg q6h								
Mean	2 68	2 3	0 14	4 9	1 9	4 1	0 49	3 6
S D	1 32	0 9	0 06		1 0	1 8	0 23	1 6
Range	1 30 5 10	1 4	0 04-0 23	3 0 16 2	1 0-4 2	1 9 7 2	0 23-0 84	1 , 6 4
n = 10								
300 mg q6h								
Mean	3 26	2 1	0 16	4 4	2 2	4 7	0 51	4 ?
S D	1 46	1 0	0 09		1 0	2 1	0 27	1 9
Range	1 39 5 45	1 4	0 06-0 32	2 2 12 3	1 2 3 9	2 6-8 5	0 25 0 96	2 , 5
n = [illegible]								
400 mg q6h								
Mean	3 33	2 5	0 19	3 6	2 3	6 3	0 86†	6 6†
S D	1 35	1 3	0 10		1 5	3 3	0 34	2 5
Range	1 90 5 10	1-4	0 10 0 31	2 3 6 9	1 1 4 5	2 8 10 3	0 ,, 1 20	4 1 9 1
n = 4								

*Two patients were studied at two dosage levels one at doses of 200 and 300 mg every 6 hours, and the other at doses of 300 and 400 mg every 6 hours

†n = 3 No urine collection was obtained in one patient

Abbreviations K = elimination rate constant $t_{1/2}$ = half life Vd = volume of distribution TBC = total body clearance RCR = renal clearance rate NRCR = nonrenal clearance rate

Initial estimates were obtained by graphical techniques The elimination rate constant (K) the volume of distribution (Vd) the total body clearance (TBC) renal clearance rate (RCR) and nonrenal clearance rate (NRCR) were calculated by simultaneous fit of the serum concentration time and urinary excretion data Quinidine renal clearance rates calculated by the computer and by amount of quinidine excreted/average serum concentration were in good agreement Nonrenal clearance was the difference between total body clearance and renal clearance The half life of elimination was determined by the formula $t_{1/2} = 0693/K$ where $t_{1/2}$ is the half life in hours and K is the elimination rate constant in hours Standard statistical tests including paired and non paired t tests multiple linear regression analyses and chi square statistics were performed using a Hewlett Packard 9810 programmable calculator

Results

Pharmacokinetic data Data for a typical patient receiving quinidine 200 mg every 6 hours are shown in Fig 1 In this patient quinidine was being discontinued The last dose was given at time zero and blood levels were followed for 24 hours The figure shows the good fit obtained between the computer estimated serum concentrations *(solid line)* and the actual serum levels *(circles)* as assayed in the laboratory It is worth noting that the quinidine disappearance curve remained linear for the three half lives followed in this patient suggesting that the one compartment open model used to fit the data is appropriate

Composite pharmacokinetic data for the patients studied are shown in Table I The average peak serum quinidine level during the six hours after a dose was 2 68 μg/ml in the patient group receiving 200 mg every 6 hours 3 26 μg/ml in the group receiving 300 mg every 6 hours and 3 33 μg/ml in the group receiving 400 mg every 6 hours There was a wide range in the peak levels at each dose The peak level in the three patient groups was attained in a mean of 2 2 hours (range 1 to 4 hours) after the dose Very little difference was found in the time to peak volume of distribution or per cent quinidine excreted unchanged in the urine at the three dosage levels Serum

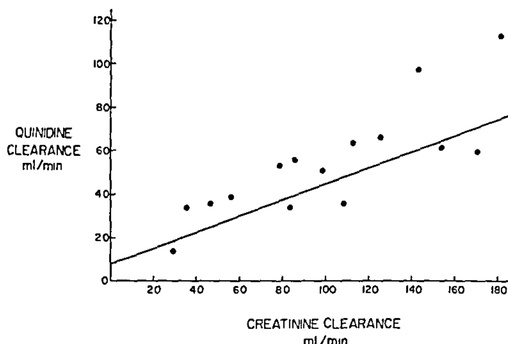


Fig 2 Quinidine clearance and creatinine clearance in 15 patient *Each circle* denotes the data from one patient A significant correlation was found (r = 0 8C p < 001) bet veen the renal clearances of creatinine and quinidine with a slope of 0 45

samples obtained during 20 dosage intervals were studied to determine quinidine binding The free fraction of quinidine averaged 31 4 ± 10 3% (mean ± 1 S D) in this population

The mean quinidine half life for the entire group of patients was 4 5 hours but there was a wide range of half lives from a low of 2 2 to a high of 16 2 hours The mean half life was 4 9 hours in the patients receiving 200 mg every 6 hours 4 4 hours in the patients receiving 300 mg every 6 hours and 3 6 hours in the patients receiving 400 mg every 6 hours The mean total body clearance (TBC) values for the patients receiving 200 300 and 400 mg every 6 hours were 4 1 4 7 and 6 3 ml /min /Kg respectively

Four patients receiving 200 mg every 6 hours were studied both during the first dosage interval and during a dosage interval at steady state In all four patients (Table II) the TBC was considerably less at steady state than during the first dosage interval The average decrease in TBC at steady state was 30% which agrees closely with the decrease in non renal clearance of quinidine in these patients

Several patients were treated concomitantly with one or more of the following extensively metabolized drugs lidocaine propranolol isoniazid diazepam and flurazepam The percentage of patients treated with these highly metabolized drugs in the three quinidine dosage groups (200 300 and 400 mg every 6 hours) was 40 57 and 100% respectively

Table II Total body clearance and nonrenal clearance rate of quinidine after the first dose and at steady state

	Dose of 200 mg every 6 hours			
	First dose		Steady state	
Patient no	*TBC (mL/min /Kg)*	*NRCR (mL/min / Kg)*	*TBC (mL/min /Kg)*	*NRCR (mL/min /Kg)*
2	7 8	7.3	5 3	4.8
13	6 3	6 0	3 0	2 7
14	5 1	4 6	4 4	3.5
17	8 0	7 7	7.2	6 4
Mean	6 8	6 4†	5 0	4 4†
S D	1.3	1 4	1.8	1 6

p < 10
†p < 05
Abbreviations TBC = total body clearance NRCR = nonrenal clearance rate

Renal clearance of quinidine Th...

Table III Rate of quinidine elimination in patients with normal and abnormal echocardiographic left ventricular diastolic dimensions

Pt	NYHA Class	K (hr)	t½ (hr)	LVID (cm)	EF (%)
LVID < 5.5 cm					
1	2	13	5 2	4 0	83
2	2	23	3 0	4 8	93
3	1	.32	2 2	5 4	53
4	1	23	3 0	5 0	66
5	1	08	9 3	5 0	53
6	2	17	4 2	5 0	—
7	1	31	2 3	5 2	47
Mean ± 1 SD		21 ± 09	4 2 ± 2 5	4 9 ± 0 4	66 ± 19
LVID > 5 5 cm					
8	4	15	4 5	7 2	36
9	2	12	5 6	6 3	14
10	1	12	5 9	8 2	57
11	3	18	3 8	6 2	54
12	1	10	7 2	6 2	41
13	2	04	16 2	6 8	31
14	1	10	7 1	5 7	44
15	3	09	8 2	8 5	37
16	1	11	6 3	6 0	49
Mean ± 1 SD		11 ± 04	7 2 ± 3 6	6 8 ± 1 0	40 ± 13

p = < 02

Abbreviations LVID = echocardiographic left ventricular internal dimension in diastole NYHA Class = New York Heart Association Functional Classification for congestive heart failure K = elimination rate constant t½ = half life EF = echocardiographic ejection fraction Pt. = patient

nary excretion of quinidine for the entire group of patients was 11 3% (range 5 4 to 25%) The mean urinary excretion at each of the three dosage levels (200 300 and 400 mg every 6 hours) was 12.2 ± 5 9 10 1 ± 2 7 and 11 6 ± 0 9% respectively The renal clearances of creatinine and quinidine were compared in 15 patients in the study These patients had creatinine clearances ranging from 29 to 180 ml /minute and quinidine clearances ranging from 14 to 98 ml /minute The mean creatinine clearance in these patients was 103 ± 48 ml /minute and the mean quinidine clearance was 55 ± 27 ml /minute A significant correlation was found (r = 0 86 p < 0 001) between the renal clearances of creatinine and quinidine by linear regression with a slope of 0 45 (Fig 2)

Quinidine in patients with hepatic disease Of the patients studied seven of 19 were chronic alcoholics but none had clinical or laboratory evidence of hepatic insufficency There were no differences in pharmacokinetic data in alcoholic compared with nonalcoholic patients However we did have the opportunity to study a 57 year old man with colonic carcinoma metastatic to the liver chronic severe congestive heart failure and markedly abnormal liver function tests who was referred with the clinical diagnosis of quinidine toxicity He had been treated with quinidine 200 mg every 6 hours for ventricular premature beats In this patient the serum quinidine level 12 hours after the last dose was 5 5 µg/ml and the half life was markedly prolonged (49 5 hours)

Quinidine in patients with altered cardiac function Five of 19 patients were in New York Heart Association Functional Class 3 or 4 for congestive heart failure The pharmacokinetic data in these patients showed no significant differences from the data obtained in patients with lesser degrees of congestive failure However when we compared patients with echocardiographic left ventricular diastolic dimensions ($LVID_D$) greater and less than 5 5 cm (Table III) we found that the elimination rate constant for quinidine was significantly lower in the patients with $LVID_D > 5$ 5 cm (K = 0 11 hr^{-1}) than in patients with $LVID_D < 5$ 5 cm (K = 0 21 hr^{-1} p < 02) The half life which is a non linear function derived from the elimination rate constant was longer in the patients with $LVID_D > 5$ 5 cm than in those with $LVID_D < 5$ 5 cm (7 2 vs 4 2 hrs p < 10)

Discussion

Despite the extensive clinical use of quinidine there are few studies available which assess quinidine pharmacodynamics in patients receiving the drug for standard clinical indications The patients reported in the present study were hospitalized in a coronary care unit and quinidine had been prescribed by their physicians for the treatment of ventricular arrhythmias In this clinical situation it was not possible to carry out the type of classic pharmacokinetic experiment that can be performed in healthy volunteer subjects—i e sequential single doses of varying size could not be administered to each subject with a prolonged washout phase allowed between doses On the other hand the clinical setting of the present report resembles more closely the settings in which quinidine is administered by the practicing cardiologist

The quinidine assay employed in this study is a new and specific HPLC method recently developed in our laboratory. This assay separates quinidine from dihydroquinidine a contaminant which is pharmacologically active.[11] The argument could be made that dihydroquinidine should be included in measured quinidine levels. However the ratio of dihydroquinidine to quinidine in serum was only about 5% and like others[1] we could find no important differences in the kinetics of the two compounds. The assay also excludes the known metabolites of quinidine. There is little evidence that these metabolites are pharmacologically active in man but antiarrhythmic activity has been reported in mice and rabbits.[11]

Recently data have been presented which are consistent with non linear quinidine pharmacokinetics[1]—i.e. doubling the dose would result in a greater than twofold increase in serum level. A possible explanation for this phenomenon is that higher doses exceed the metabolic capacity of the liver. Our data in four patients treated with quinidine 200 mg every 6 hours who were studied both after the first dose and at steady state are consistent with this hypothesis (Table II). Compared to the first dose there was a 30% reduction in total body clearance at steady state which was attributed to a decrease in the non renal clearance of the drug. This suggests that there may be a limited capacity for hepatic enzymatic metabolism of quinidine which is exceeded at higher serum levels. An alternate explanation is that the first dose values for drug elimination are artificially elevated because the distribution phase is not yet complete. In either case our findings and those of others demonstrate a poor correlation between single dose studies and steady state results. Thus in order to be clinically useful pharmacokinetic studies of quinidine should be carried out at steady state.

The steady state pharmacokinetic values reported in this paper were obtained from three groups of patients who were receiving quinidine in doses of 200, 300 or 400 mg every 6 hours (Table I). It is intriguing that there was only a slight increase in the mean peak serum quinidine concentration in the three groups at the three dose levels studied. The shorter half life and greater total body clearance of quinidine at the higher doses suggest more rapid quinidine metabolism in the patients receiving the higher doses. Since these patients were titrated to higher doses by their physicians patients with an intrinsically greater ability to metabolize quinidine may have received the higher doses for therapeutic reasons. Lower doses of quinidine could have resulted in low serum levels and presumably in an inadequate therapeutic effect resulting in an increase in dose by the clinician. Interestingly the percentage of patients receiving other highly metabolized drugs was greater in the groups receiving higher doses of quinidine: 40%, 57% and 100% in the groups receiving 200, 300 and 400 mg every 6 hours. Our study does not permit analysis of drug interactions but this possibility should be considered in future studies.

We found the mean half life of quinidine in the entire group of patients to be 4.5 hours. Previous investigators have reported mean half lives of 4.3 to 7.8 hours. The individual values for quinidine half life in our patients ranged from 2.2 to 16.2 hours which is comparable to the range of 3 to 19 hours found by Kessler and co workers.

The free fraction of quinidine in the present study averaged 31.4 ± 10.3% which is somewhat larger than the average of 23.3% reported recently in healthy human volunteers.[1] Factors which should be considered in evaluating this increase in free drug concentration are the older age of our patients, the presence of organic disease and the concomitant administration of other drugs. It is also possible that serum storage in Vacutainers prior to assay may have been responsible for an increase in the apparent free drug concentration.

The urinary excretion of quinidine in the present study averaged 11.3%. This is comparable to the value of 13% and 10.7% urinary excretion after oral administration reported in two recent studies which also used specific quinidine assays. Urinary excretion values obtained with the less specific double extraction method have ranged from 23 to 36%. This appears to reflect the failure of that assay method to exclude quinidine metabolites. We found a significant correlation ($r = 0.86$, $p < .001$) between the renal clearances of quinidine and creatinine with the quinidine clearance approximating half of the creatinine clearance (Fig. 2). Thus while only about 10% of the quinidine dose is excreted unchanged in the urine the amount excreted by this route is closely related to the excretion of creatinine.

It is intriguing that the elimination rate constant for quinidine was significantly less in patients with echocardiographic left ventric-

diastolic dimensions > 5.5 cm than in those with $LVID_D$ < 5.5 cm. This separation of patients was not obtained when the patients were classified according to clinical severity of congestive heart failure. It is tempting to speculate that impaired left ventricular function, through a reduction in hepatic blood flow, could lead to a decreased rate of quinidine metabolism, as has been suggested for lidocaine.

Clinical implications. The findings in the present study have several possible clinical implications.

1. The wide range of quinidine half lives (2.2 to 16.2 hours) emphasizes the necessity of individualizing quinidine dosages regimens. The mean half life was 4.5 hours; patients with half lives shorter than the mean may require dosing more often than every 6 hours.

2. The elimination rate constant for quinidine was significantly less in patients with echocardiographic left ventricular diastolic dimensions > 5.5 cm than in those with $LVID_D$ < 5.5 cm. This suggests that patients with left ventricular dilatation may be at increased risk for quinidine toxicity. Such patients may be identifiable with echocardiography.

3. The average urinary excretion of quinidine was only 11.3%. This supports the suggestion of others that quinidine dosage may not need to be altered in the presence of renal insufficiency.

4. Quinidine must be administered with caution to patients with hepatic insufficiency. These patients may have remarkably abnormal pharmacokinetic features, as illustrated both by our patient with congestive heart failure, liver metastases, quinidine toxicity, and a half life of 49.5 hours, and by Conrad's patient[1] with cirrhosis, hepatorenal syndrome, and a quinidine half life of 53 hours.

Summary

Quinidine serum levels and pharmacokinetic data were assessed during steady state therapy with oral quinidine sulfate in 19 hospitalized patients who were being treated for ventricular arrhythmias. A new high performance liquid chromatography assay was employed. Four patients were studied both after the first dose of quinidine and at steady state and the initial dose pharmacokinetic values were found not to be predictive of steady state.

The mean half life of quinidine was 4.5 hours, but there was wide individual variation. The elimination rate constant for quinidine was significantly lower in patients with echocardiographic evidence of left ventricular dilatation than in patients with normal echocardiographic left ventricular size. The average urinary excretion of quinidine was only 11.3%. The pharmacokinetic data in seven chronic alcoholic patients without clinical or laboratory evidence of hepatic insufficiency did not differ from the data obtained in nonalcoholic patients. However, with severely impaired liver function, there may be marked prolongation of quinidine half life predisposing to quinidine toxicity. The possible clinical implications of these findings are discussed.

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The nature and prevalence of the abnormal exercise electrocardiogram in mitral valve prolapse

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Mitral valve prolapse is a common disorder many of whose features mimic those of coronary artery disease The tendency for individuals with mitral valve prolapse to develop exercise induced ECG repolarization abnormalities is one such feature as has been previously recognized[1]

The prevalence of an abnormal exercise ECG response in this syndrome is unknown

At the United States Air Force School of Aerospace Medicine (USAFSAM) military air crew members are referred for evaluation of possible cardiac disorders particularly those capable of producing sudden incapacitation in flight such as coronary artery disease This evaluation routinely includes complete noninvasive cardiac assessment including electrocardiogram vector cardiogram chest x ray echocardiogram phono cardiogram ambulatory ECG monitoring and maximal treadmill exercise stress testing Those aircrew members receiving waivers for continued aviation duties are re evaluated on an annual basis and thus may undergo multiple annual treadmill tests All individuals with unexplained ST segment abnormalities on treadmill testing are offered coronary arteriography and left ventricular cineangiography The observation that several subjects with abnormal treadmill tests had angiographic and other features of mitral valve prolapse in the absence of angiographically demonstrable coronary artery disease led us to explore retrospectively the relationship between mitral valve prolapse and ECG repolarization abnormalities on treadmill exercise testing

Material and methods

The clinical records of all aircrew members referred to USAFSAM for medical evaluation since 1971 were reviewed in an effort to isolate individuals with mitral valve prolapse (MVP) as defined by the fulfillment of two of the three following criteria (1) auscultatory and/or phono cardiographic evidence of mitral valve prolapse namely midsystolic click late systolic murmur or both with appropriate responses to physical and pharmacological interventions (2) typical echo cardiographic abnormalities including systolic posterior buckling and holosytolic posterior hammocking of the mitral valve echo (with care taken to avoid caudad angulation of the ultrasound transducers) and (3) abnormal systolic ballooning or billowing of either leaflet of the mitral valve into the left atrium during a sinus beat visualized with right anterior oblique left ventricular cineangiography All patients with mitral valve prolapse diagnosed on the basis of angiographic findings were so classified on the basis of quantitative angiographic criteria Echocardiography was performed on a commercially available Ekoline 20 ultrasonoscope interfaced with an Electronics for Medicine VR 6 strip chart recorded Cardiac catheterization was performed utilizing standard techniques including selective coronary arteriography by the techniques of either Judkins or Sones All patients

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were maximally exercised utilizing a modification of the Balke Ware protocol (USAFSAM Tread mill Protocol) reported previously [11] An abnormal or positive repolarization response was defined as at least 0 1 mv of horizontal or down sloping ST segment depression for 0 08 sec after the inscription of the J point Standard bipolar Leads X (CC) and CM, as well as an inferior Lead Yh, and an inferior posterior Lead Z were continuously monitored with the patient supine during three minutes of quiet standing during 30 seconds of supine hyperventilation throughout treadmill exercise and during an eight minute supine recovery period All signals were recorded continuously on hard copy and on magnetic tape for storage and playback

For the purposes of analysis the first three minutes of the exercise period were defined as early exercise the last three minutes as peak exercise and the remainder of the exercise period was defined as mid exercise Similarly the first three minutes of recovery were defined as early recovery the last three minutes as late recovery and the mid portion as mid recovery In addition to the data from patients with clinical evidence of mitral valve prolapse the treadmill tests of 24 consecutive patients with abnormal treadmill tests presumably due to obstructive coronary artery disease found at catheterization (CAD group) and of 21 consecutive patients (normal group) with abnormal treadmill tests and no apparent cardiac disease (i e no evidence of coronary artery disease or mitral valve prolapse at cardiac catheterization) were examined

Statistical analysis was performed utilizing a two-tailed Student s t test

Results

Patient characteristics Forty three patients met our stated criteria for the diagnosis of mitral valve prolapse (Table I) Of the 43 patients in group P 23 had phonocardiographic and echocardiographic evidence of mitral valve prolpase Because of the absence of symptoms and ECG abnormalities these 23 patients did not have angiography performed Of the 20 patients with left ventricular angiogram (all of which demonstrated mitral valve prolapse) eight also had both abnormal echocardiogram and auscultatory abnormalities and six others had phonocardiographic and/or auscultatory confirmation of mitral valve prolapse with normal echocardio

ı the remaining s x patients no ausculta phonocardiographi evidence of mitral lapse could be elicited despite repeated on ı upine standing squatting and ıl de ubitus po ı ions These six patients r ı ı t echocardiographic and angiograp dı ı of acoustically silent mitral valve ı

I n ı nts were male (mean age 36 years) ı ı ı 43 patients in group P were referred ı ı uat n of au cultatory abnormalities 14 eca ı f ECG abnormalities (four with complet r ght bundle branch block two with f st o se ond-degree A V block two with r tı ul r premature beats one with an isolated ei rde) atrial fibrillation and five with minor ı aspecific repolarization abnormalities) and ght pı ients were referred for reasons unrelated tı thı ı ardiova cular system Only three patients ı ere referred to USAFSAM because of an abnor m ıl treadmill exercise test performed elsewhere Thirty ı ine of the 43 patients were completely asymptomatic four had chest pain and/or palpitations neither of which was considered disabling or requiring medical attention Thirteen patients had musculoskeletal abnormalities detected radiologically or clinically including pectus excavatum loss of normal thoracic dorsal kyphosis and exaggerated thoracic scoliosis In 42 of the 43 patients mitral valve prolapse was the only cardiovascular abnormality in one patient there was hemodynamically insignificant aortic regurgitation associated with a congentially bicuspid aortic valve No patient was hypertensive or hypokalemic and none was taking any regular medication Of the 20 patients undergoing cardiac catheterization 16 had selective coronary arteriography (including the three patients with chest pain) all coronary arteriograms were entirely normal

Analysis of treadmill tests At the time of initial treadmill stress testing 35 patients had a normal resting electrocardiogram seven had minor repolarization abnormalities and one had complete right bundle branch block None of the patients had resting ST segment abnormalities A total of 82 treadmill exercise tests were available for review for the 43 patients The peak heart rate achieved was 186 ± 13 beats per minute (mean ± 1 standard deviation) Only two of the efforts were submaximal and only four were associated with a hypertensive blood pressure

Table I Clinical characteristics of 43 patients with mitral valve prolapse

Patient	Age	Auscultation	Echo	Angiography	Symptoms	Musculoskeletal abnormalities	ECG	TMT
1	33	MSC	Late syst	PPML	None	–	Flat T V, V	Abnormal
2	28	MSC LSM	Holosyst	–	None	–	Normal	Normal
3	37	MSC LSM	Late syst	–	None	–	Flat T 2 3aV$_F$	Normal
4	34	MSC	Holosyst	–	None	–	Normal	Abnormal
5	34	MSC LSM	Late syst	–	None	–	Normal	Normal
6	42	LSM	Late syst	–	None	–	Normal	Normal
7	49	MSC LSM	Late syst.	–	None	–	Normal	Normal
8	30	Normal	Late syst	PPML	None	–	Normal	Abnormal
9	36	MSC	Holosyst	PPML	None	–	Normal	Abnormal
10	39	MSC LSM	Holosyst	–	None	–	Normal	Normal
11	27	LSM	Late syst	–	None	Pectus straight back	Normal	Normal
12	35	MSC LSM	Late syst	–	Palpitations	–	Normal	Abnormal
13	39	MSC	Late syst.	PPML	None	–	CRBBB	Abnormal
14	24	Normal	Holosyst	PPML, PAML	None	Pectus straight back	Normal	Normal
15	31	HSM	Late syst	–	None	–	Normal	Normal
16	33	MSC LSM	Holosyst	–	Chest pain palpitations	–	Normal	Normal
17	41	MSC LSM	Late syst	–	None	–	Normal	Normal
18	45	MSC	Normal	–	None	Scoliosis	Flat T 2,3,aV$_F$	Abnormal
19	38	LSM	Holosyst	–	None	–	Normal	Normal
20	44	Normal	Late syst	PPML	None	–	Normal	Abnormal

Abbreviations MSC = midsystolic (nonejection) click LSM = late systolic murmur HSM = holosystolic murmur Late Syst = late systolic posterior buckling of mitral valve echo Holosyst. = holosystolic "hammocking" of mitral valve echo PPML = prolapse of posterior mitral leaflet PAML = prolapse of anterior mitral leaflet MR = mitral regurgitation ECG = electrocardiogram TMT = repolarization response to maximal treadmill testing NA = not available

response as judged by previously published heart rate and blood pressure criteria for normals utilizing the USAFSAM protocol

Of the 43 patients with mitral valve prolapse 12 (28%) had an abnormal initial treadmill exercise test Of the nine patients with abnormal exercise repolarization responses who had more than one exercise test six did not have reproducibly abnormal responses None of the patients had chest pain at any time during exercise testing

Closer analysis of the data from abnormal exercise tests (Table II) revealed that in all 12 patients the supine electrocardiogram was free of ST segment and T wave abnormalities In ten of 12 (83%) ST segment and/or T wave changes developed with assumption of the standing position These repolarization abnormalities did not increase and usually regressed during and following the hyperventilation period All exercise tests were definitely abnormal during the mid portion of exercise greater than 2 mm of ST depression was present in two of 12 patients ST segment depression persisted through peak exercise in only 33% of patients and through the immediate recovery period in only 8% No specific pattern of lead positivity was demonstrated with seven of 12 tests being positive in more than one lead Only two of the 12 patients had an exercise test which was abnormal in Lead Yh only No patient had ST depression in Lead Z

Analysis of the pattern of positivity of the treadmill tests in the CAD group and in the normal group (Table II) revealed that significantly fewer of the patients in these two groups developed ST segment or T wave abnormalities

Table I continued

Patient	Age	Auscultation	Echo	Angiography	Symptom	Musculoskeletal abnormalities	ECG	TMT
21	34	MSC LSM	Late syst	–	None	–	Normal	Normal
22	44	MSC	Late syst	–	Chest pain	–	Normal	Normal
23	55	MSC	Late Syst	PPML	None	–	Normal	Abnormal
24	[illegible]	LSM	NA	PPML, MR	None	–	Normal	Normal
25	44	MSC	Late syst	–	None	–	Normal	Normal
26	26	LSM	Holosyst	PPML, MR	None	–	Normal	Normal
27	[illegible]	Normal	Holosyst	PPML	None	Scoliosis	Normal	Normal
28	41	MSC	Late syst	–	None	Scoliosis	Normal	Normal
29	43	LSM	Holosyst	–	None	–	Normal	Normal
30	28	MSC	Holosyst	–	None	–	Normal	Normal
31	43	LSM	Late syst	–	None	–	Normal	Normal
32	30	MSC	Holosyst	–	None	Scoliosis	Normal	Normal
33	[illegible]	MSC	Holosyst	–	None	Scoliosis	Inverted T 2,3aV	Normal
34	45	MSC LSM	Late syst	PPML	None	Pectus	Normal	Normal
35	[illegible]	MSC	Holosyst	–	None	Pectus	Normal	Normal
36	53	MSC	Normal	PPML	Chest pain Palpitations	Pectus	Normal	Normal
37	24	LSM	Late syst	PPML	None	Pectus Scoliosis	Normal	Normal
38	40	MSC	Normal	PPML	None	–	Normal	Normal
39	40	Normal	Late syst	PPML	None	Scoliosis	Normal	Abnormal
40	25	Normal	Holosyst	PPML	None	Pectus	Normal	Abnormal
41	40	MSC	Late syst	PPML	None	–	Normal	Abnormal
42	40	MSC	Normal	PPML	None	–	Normal	Normal
43	[illegible]	MSC LSM	Late syst	PPML, PAML, MR	None	–	Normal	Normal

upon standing In addition the tendency towards normalization of the ST segment response during peak exercise and early recovery (Fig 1) noted in the patients with mitral valve prolapse was considerably less common in the other two groups

Two additional trends were noted when the results of the treadmill test were examined in the light of auscultatory findings Of the 43 patients (Table I) 20 were found to have auscultatory or angiographic evidence of mitral regurgitation while 23 patients had no such evidence Of the 12 patients with abnormal treadmill tests only one was found to occur in a patient with evidence of mitral regurgitation The other 11 patients with abnormal repolarization responses to maximal treadmill exercise were among those without evidence of mitral regurgitation Furthermore four of these 11 patients were among the six patients in the entire group with angiographically documented acoustically silent mitral valve prolapse (Fig 2)

Discussion

Prevalence of abnormal treadmill tests Previous investigations dealing with exercise testing in patients with mitral valve prolapse have emphasized the occurrence of exercise induced arrhythmias in this condition However an association between mitral valve prolapse and ischemic ST segment responses to treadmill or bicycle exercise testing has been noted[1] Although the prevalence of abnormal treadmill test in these studies varied from 0 to 60% of the 159 cases reported in these series in which exercise stress testing was performed 52 were interpreted as positive resulting in an over all prevalence of abnormal exercise test of 33% This figure is comparable to the 28% reported in the present study In order to determine whether these find

Table II Treadmill exercise test results

	Number (%) of patients		
	MVP ATM (n = 12)	*CAD ATM (n = 24)*	*ATM only (n = 21)*
Standing ECG changes	10 (83)	7 (29)	9 (43)
Positive early exercise	8 (67)	4 (17)	6 (28)
Positive mid exercise	12 (100)	16 (67)	17 (81)
Positive peak exercise	4 (33)	18 (75)	14 (67)
Positive early recovery	1 (8)	9 (38)	3 (14)
Positive mid recovery	4 (33)	17 (71)	8 (38)
Positive late recovery	6 (50)	15 (63)	12 (57)
Standing ECG changes + positive early mid exercise + negative peak exercise and early recovery	7 (58)	0 (0)	1 (5)
>2 mm ST depression	2 (17)	11 (46)	9 (43)

Abbreviations MVP = mitral valve prolapse CAD = coronary artery disease ATM = abnormal treadmill exercise test
= $p < .05$ vs Group with MVP
= $p < .01$ vs. Group with MVP
= $p < .002$ vs. Group with MVP

ings reflected a true increase in the prevalence of positive treadmill tests in mitral valve prolapse we reviewed the records of the USAFSAM Exercise Laboratory and found that over the period encompassed by the study 2 171 asymptomatic apparently healthy men (mean age 40 years) were exercised in our laboratory for the first time 158 (7%) of whom had exercise induced repolarization abnormalities Thus mitral valve prolapse results in at least a fourfold increase from the expected prevalence of false positive treadmill tests in asymptomatic individuals The results of the present study may actually underestimate the true prevalence of abnormal treadmill tests in patients with mitral valve prolapse since the 2 171 patients mentioned above included those with resting ECG abnormalities and since this study was restricted to male patients without resting ST segment abnormalities

Little is known regarding the true reproducibility of exercise induced abnormalities The fact that only three of the nine patients with mitral valve prolapse and abnormal treadmill tests in this study who were retested had completely reproducible repolarization responses is not surprising in view of what previous work has been done in normal subjects and in patients with coronary artery disease[13,14] in which investigators have noted non reproducible ST depression in from 10 to 60% of individuals Alternatively the lack of reproducibility in the present study could be related to the dynamic nature of the lesion marked variations in physical findings and other manifestations of mitral valve prolapse are known to occur with repeated examinations

Pathophysiology of exercise induced ECG abnormalities The mechanism of exercise induced repolarization abnormalities in mitral valve prolapse has not been discussed extensively in the existing literature Many of the features of the mitral valve prolapse syndrome such as chest pain ventricular arrhythmias and resting T wave abnormalities are felt to be ischemic in origin Several theories explaining ischemia in mitral valve prolapse have been forwarded but the concept which seems to have gained general acceptance postulates that the voluminous mitral leaflets during their systolic excursion into the left atrium produce abnormal tension within the chordae tendineae and the papillary muscles to which they are attached as well as the surrounding myocardium Although the existing data are inconclusive several radionuclide studies have documented the presence of perfusion defects at rest and following exercise in patients with mitral valve prolapse in the absence of coronary artery disease[16,17] It is tempting to speculate that in the exercising individual with mitral valve prolapse positive inotropic influences and decreased left ventricle afterload lead to an increase in systolic emptying and to a more violent ventricular assault on the mitral valve This in turn could lead to an increase in mitral valve prolapse and in the abnormal papillary tug presumably responsible for myocardial ischemia Of interest in this regard is the observation in the present study of a decreased prevalence of exercise induced ECG repolarization abnormalities in patients with evidence of mitral regurgitation Even severe mitral regurgitation is known to be compatible with a long asymptomatic period because of the tendency of this lesion to reduce tension developed by the left ventricular myocardium It is

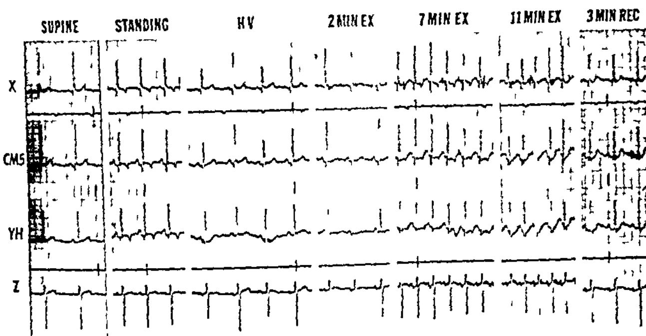


Fig 1 Portions of exercise ECG from patient No 40 demonstrating the pattern of ECG abnormalities typical of our population Note prominent T wave changes with assumption of standing position ST depression at mid-exercise with normalization during peak exercise and recovery *HV* = hyperventilation *2 MIN EX* = second minute of exercise *7 MIN EX* = seventh minute of exercise *11 MIN EX* = eleventh minute of exercise *3 MIN REC* = third minute of recovery

known that under experimental circumstances even massive mitral regurgitation does little to increase total myocardial oxygen consumption therefore it is not inconceivable that in the exercising human with mitral valve prolapse the presence of mild mitral regurgitation might reduce myocardial oxygen consumption and lessen the tendency for the development of myocardial ischemia

Mitral valve prolapse and vasoregulatory abnormalities An especially significant finding was that of the pattern of positivity of the exercise induced repolarization abnormalities among our patients with mitral valve prolapse The majority of our patients with both abnormal treadmill tests and mitral valve prolapse demonstrated ST segment and/or T wave changes with the assumption of the standing position ST segment depression (usually less than 2 mm) during the early and mid portion of the exercise period absence of ST segment depression during peak exercise and immediate recovery with or without reappearance of ST segment abnormalities during late recovery This pattern was found in 58% of the study patients with mitral valve prolapse and was found in only one of 45 other patients with abnormal treadmill tests without mitral valve prolapse This pattern bears a striking resemblance to that found in a group of 40 patients with vasoregulatory abnormalities described by Friesinger and associates[20] These investigators published a report concerning 40 patients the majority of whom had either chest pain with normal coronary arteriograms or neurocirculatory asthenia and in whom ischemic electrocardiographic changes were noted during standing and during the early portion of treadmill exercise tests The patients were young (mean age 34 years) and were lacking in risk factors for coronary artery disease The ischemic electrocardiographic changes were postulated to occur on the basis of an abnormal autonomic response to ordinary cardiovascular stress as evidenced by a marked increase in heart rate upon standing In view of the fact that all of Friesinger and colleagues patients were studied before 1967 and that echocardiographic auscultatory and angiographic findings were not reported upon in his patients and based upon the findings of the present study we feel there is a reasonable likelihood that many patients with vasoregulatory abnormalities have mitral valve prolapse This

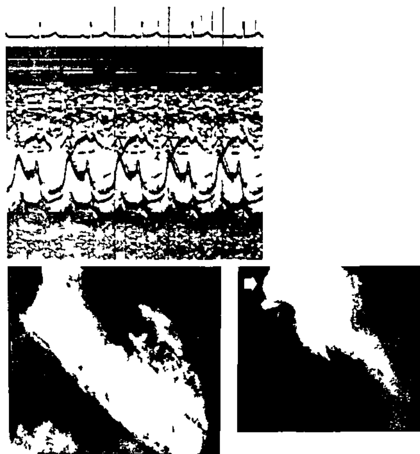


Fig 2 Echocardiogram *(top)* and end diastolic *(bottom left)* and end systolic *(bottom right)* frames of left ventricular cineangiogram from same patient as in *Fig 1* Note holosystolic echographic mitral hammocking and angiographic evidence of posterior mitral leaflet prolapse *(arrow)* This patient was one of those with acoustically silent mitral prolapse

association is not surprising when certain facts are taken into consideration First as mentioned previously many of the patients originally described by Friesinger and colleagues were felt to satisfy criteria for the diagnosis of neurocirculatory asthenia a condition characterized by atypical chest pain asthenic build and neurotic symptoms The similarity of these features with those found in mitral valve prolapse has been emphasized appropriately by Wooley and requires no further elaboration Secondly as mentioned previously all of Friesinger and associates patients were studied over a decade ago at which time general awareness of the mitral valve prolapse syndrome was lacking the majority of the patients in the original description of Friesinger and co workers did not have angiography performed and none had echocardiograms

The most important observation linking these groups of patients is that of the standing electrocardiographic changes Orthostatic T wave abnormalities in patients with mitral valve prolapse have been briefly commented upon by previous investigators Pharmacologic and physical interventions which decrease left ventricular volume are known to result in an increase in mitral valve prolapse and the assumption of the standing position is one of the purest examples of this phenomenon It seems reasonable therefore to assume that the standing T wave abnormalities observed in our patients are the consequence of increased tension on the papillary muscles brought about by the increase in ventriculovalvular disproportion which occurs with standing The observation by Friesinger and associates that ischemic electrocardiographic responses to exercise were corrected in many cases by maneuvers which increased left ventricular volume (the administration of propranolol application of body stockings and Valsalva maneuver) further supports the contention that vasoregulatory abnormalities may be a manifestation of

mitral valve prolapse The retrospective nature of the present study prevented us from confirming these observations The normalization of the ST response to treadmill exercise during the late or peak portion of the exercise period is less easily explained Although definitive studies of alterations in ventricular volume and dynamics during treadmill exercise are lacking it is interesting to note that Friesinger and colleagues account for this phenomenon on the basis of an increase in left ventricular volume secondary to increased cardiac output and venous return during the later phases of exercise This explanation is certainly acceptable in the present context as well

Silent mitral valve prolapse The presence of mitral valve prolapse is difficult to substantiate in the absence of typical auscultatory abnormalities. The criteria for the diagnosis of mitral valve prolapse in the present study were intentionally stringent so as to avoid the recent tendency toward overdiagnosis of this disorder [4] In the present study a case would not be accepted as silent mitral valve prolapse unless both echocardiographic and angiographic indications of this disorder were present We do not believe that silent mitral valve prolapse can be diagnosed with certainty in the absence of either echocardiographic or angiographic features of this disorder If the clinicopathological correlations presented by Roberts and co workers are accepted then silent mitral valve prolapse can be presumed to correspond to a minimal degree of mitral pathology The graphic manifestations of such disease are therefore not likely to be flagrant The opportunity to accurately diagnose silent mitral valve prolapse is probably more common in a laboratory in which cardiac catheterization is routinely performed in asymptomatic individuals All six of our cases were not only acoustically but also clinically silent the indication for catheterization having been an abnormal treadmill test in four out of the six cases These observations indicate that the suspicion of mitral valve prolapse in patients with an abnormal treadmill test must extend to asymptomatic patients without the auscultatory abnormalities typical of mitral valve prolapse

Clinical implications With the recent increase in the use of treadmill exercise testing as a part of a health "screening" procedure in asymptomatic individuals clinicians are increasingly confronted with the problem of exercise induced ischemic ECG changes in individuals without chest pain Our findings imply that echocardiography is indicated in such cases since even in the absence of symptoms or auscultatory abnormalities mitral valve prolapse may herald its presence in the form of exercise induced ECG repolarization abnormalities particularly of the variety currently associated with vasoregulatory abnormalities

Summary

The maximal treadmill exercise tests in 43 subjects with mitral valve prolapse were retrospectively examined and compared to those of 24 consecutive patients with abnormal maximal treadmill tests and arteriographic evidence of obstructive coronary artery disease and 21 consecutive patients with abnormal treadmill tests with evidence of neither mitral valve prolapse nor coronary artery disease at catheterization Twelve of 43 (28%) patients with mitral valve prolapse had greater than 0 1 mv of flat or downsloping ST depression during or following treadmill exercise Of these 12 patients seven (58%) were found to have the pattern of abnormal treadmill test previously described as indicative of vasoregulatory abnormalities four patients satisfied the diagnostic criteria for acoustically silent mitral valve prolapse and only one had clinical or angiographic evidence of mitral regurgitation The finding of the vasoregulatory pattern of abnormal ECG response was significantly less common in the groups with abnormal treadmill tests and coronary disease and with neither coronary disease nor mitral valve prolapse ($p < 0025$) We conclude that the finding of an abnormal treadmill test particularly of the type associated with vasoregulatory abnormalities should lead to the suspicion of mitral valve prolapse even in the absence of symptoms and typical auscultatory abnormalities

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Effect of left anterior hemiblock on exercise induced ST-T segment changes

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Exercise testing has proved to be a valuable noninvasive method of evaluating patients with chest pain.[1] The significance of exercise-induced ST depression is often difficult to determine when the resting electrocardiogram is abnormal. The presence of left bundle branch block, Wolff-Parkinson-White syndrome, and left ventricular hypertrophy renders post exercise ST segment changes rather nonspecific.[2] Exercise induced depression of the ST segment which is limited to chest Leads V to V_3 is nonspecific in the presence of right bundle branch block. However, little data are available regarding the effect of left anterior hemiblock on exercise induced ST segment changes. This retrospective study evaluates the effect of left anterior hemiblock on the sensitivity, specificity, and predictive value of the treadmill stress test.

Materials and methods

Resting electrocardiograms of all patients who underwent stress testing and coronary angiography at Creighton St. Joseph Hospital from 1975 to 1977 were evaluated. Those patients whose resting electrocardiograms showed left anterior hemiblock constituted the study group. Patients with other intraventricular conduction defects and who were receiving digitalis preparations were excluded. Left anterior hemiblock was diagnosed using the following criteria: (1) QRS frontal plane axis of −45 to −60, (2) QRS duration of less than 0.1 second, and (3) a Q S_3 pattern in the limb leads.

The study group consisted of 17 patients. There were 12 men and 5 women. The mean age was 60.8 (range 39 to 72). All patients were referred for evaluation of chest pain. Exercise testing was performed according to the Bruce protocol. The test was considered maximal in 16 patients. The remaining patient exercised for 10.3 minutes and achieved a heart rate of 143 beats/minute, which was 85% of predicted maximum. Twelve lead electrocardiograms were recorded at rest, during exercise, immediately after exercise, and at 0.5, 1, 2, 3, 4, 5, and 6 minutes after exercise. Tests were considered positive if the post-exercise electrocardiogram revealed 1 mm or more of exercise-induced flat or downward ST segment depression of 80 msec. duration. The resting and exercise electrocardiograms were interpreted by two independent observers. Selective coronary arteriographic studies were performed on all patients by the method of Sones and Shirey.[3] Seventy-five percent or greater reduction in the diameter of a coronary artery was considered to be significant stenosis.

The customary formulae were used to analyze the statistical data including chi square with Yates correction.

Results

Of the 17 patients, eight patients had positive exercise tests. Six were men and two were women. All eight had significant narrowing of one or more coronary arteries. Two pateints had single vessel stenosis, four had two-vessel stenoses, and three had triple-vessel stenoses. Nine patients had negative tests. Of these, six were true negatives

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All three patients with coronary artery disease and negative exercise tests had single vessel disease Two were women The sensitivity of exercise testing was 72 7% the specificity was 100% and the predictive value 100%

Discussion

The sensitivity specificity and predictive value of exercise testing previously reported from our institution were 53% 91% and 73% respectively[11] In comparing the present study with the previous investigation we found no statistically significant difference in the results of exercise testing in patients with and without left anterior hemiblock on the resting electrocardiogram ($P > 0.05$)

The significance of isolated left anterior hemi block in the electrocardiogram is unclear The relationship of left axis deviation to pathologic changes of myocardial fibrosis was first reported by Grant[1] Rosenbaum[9] suggested that myocar dial fibrosis involving the anterior division of the left bundle is associated with extreme left axis deviation of more than 45 degrees and that the most common etiologic factor is coronary artery disease Ostrander[3] had reported a benign prog nosis for isolated left axis deviation Miller and Naughton[4] suggested that isolated left axis deviation is not necessarily a benign finding and that the incidence of positive exercise tests is much higher compared to an age matched control with a normal frontal plane QRS axis In a more recent study Carne and associates[1] found that in men 30 years or older left anterior hemiblock was not a sensitive marker of clinical cardiac disease since this diagnosis was absent in 80% of the subjects Surawicz and Saito[1] have suggested that rightward posterior orientation of the termi nal QRS complexes can be seen in some patients with left anterior hemiblock and this may lead to false negative exercise tests These patients have in common QRS complexes with deep S wave and T waves directed opposite to the S wave in the left precordial leads In these leads the ST segments tend to slope steeply from the nadir of the S wave to the onset of the T wave and these secondary ST changes tend to cancel or obscure ST segment depression induced by myocardial ischemia Three of our patients had an RS ratio of greater than one in chest Leads V and V Two of these had true negative tests the third had a true positive test with 2 mm ST segment depression in leads V_5 and V

Although our study suggests that patients with left anterior hemiblock have significant coronary artery disease (11 out of 17 or 64%) this high incidence is probably due to the fact that the study population was highly selective having been referred to a medical center for chest pain evaluation

It is concluded that the sensitivity specificity and predictive value of the exercise tests are not significantly different in patients with left anteri or hemiblock compared to those without left anterior hemiblock

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An experimental study of release arrhythmia Occlusion time-dependent changes in ventricular fibrillation threshold

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It is well known that ventricular arrhythmia occurs frequently during acute coronary occlusion Nevertheless it is only recently that interest has been taken in the occurrence of ventricular arrhythmia after reperfusion following coronary occlusion[1] The latter kind of arrhythmia is termed release arrhythmia or reperfusion arrhythmia but it is not yet clearly defined In the case of this arrhythmia antiarrhythmic agents such as lidocaine and β blockers are reported not to be effective[2] Hence the mechanism of release arrhythmia is believed to be different from that of the ordinary arrhythmia although the details of the mechanism of release arrhythmia remain obscure

To investigate the mechanism of the release arrhythmia we studied the effect of the duration of occlusion time on the recovery time courses of the VMRT (Ventricular Multiple Response Threshold) and changes in serum electrolytes

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Methods

Twenty-one adult mongrel dogs, of both sexes and weighing between 9 and 15 kilograms were used After anesthetization the chest was opened with a fourth intercostal incision and the heart was suspended in a pericardial cradle Silk ligation was performed at a branch of the left anterior descending artery Dogs were divided into three groups of seven animals each according to the duration of coronary occlusion time Group I with 10 minutes of occlusion group II with 15 minutes of occlusion and group III with 30 minutes of occlusion Each group was placed under observation until 40 minutes after reperfusion of the preceding occlusion

For the measurement of VMRT a platinum bipolar stimulating electrode with 3 mm interpolar distance was attached to the apex of the left ventricle As we have described previously[3] VMRT was measured at the minimum current necessary to induce more than three serial ventricular beats Venous blood returning mainly from the ischemic region was taken from the great cardiac vein at the place just beneath the left auricle and arterial blood was taken from the femoral artery Time courses of VMRT and A V difference in several serum electrolyte concentrations—K Na Cl and Ca were measured Heart rate and serum pH were also measured before during and after release of coronary ligation

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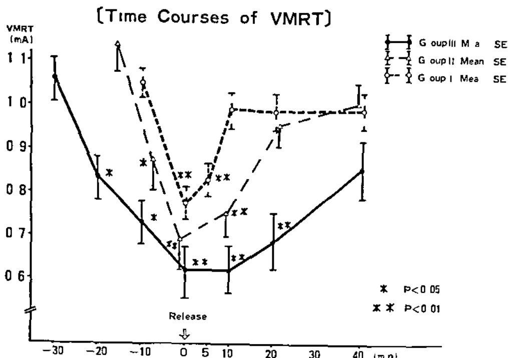


Fig 1 Time courses of VMRT are shown In any group after ligation VMRT was decreased significantly However its recovery time course was different the longer the occlusion time the longer was the recovery time

Results

In Fig 1 the time courses of VMRT for group I II and III are shown In group I the initial mean value of 1 05 ± 0 03 mA (mean ± standard error) significantly decreased to 0 78 ± 0 05 mA after 10 minutes of occlusion A decreased value of 0 83 ± 0 05 mA was still observed at 5 minutes after reperfusion but recovery to the initial value was observed at 10 minutes after reperfusion and was maintained thereafter In group II the initial value of 1 15 ± 0 05 mA significantly decreased to 0 88 ± 0 03 mA after 7 5 minutes of occlusion and to 0 70 ± 0 04 mA after 15 minutes of occlusion A decreased value of 0 75 ± 0 05 mA was still observed at 10 minutes after reperfusion but recovery to the initial value was observed at 20 minutes after reperfusion and was maintained thereafter In group III the initial mean value was 1 06 ± 0 05 mA This value was successively decreased to 0 84 ± 0 05 mA 0 73 ± 0 05 mA and 0 63 ± 0 05 mA after 10 20 and 30 minutes of occlusion respectively In this group decreased values of VMRT were observed even after 10 minutes and 20 minutes of reperfusion with respective values of 0 62 ± 0 06 mA and 0 69 ± 0 06 mA recovery was only after 40 minutes of reperfusion

The differences in K concentration between arterial and venous blood during the course of three experiments are illustrated in Fig 2 In group I the initial mean A V difference of 0 18 ± 0 03 mEq /L (Mean ± S E) significantly decreased to −0 21 ± 0 07 mEq /L after 10 minutes of occlusion Rapid recovery to the initial level was observed at 5 minutes after reperfusion demonstrating 0 23 ± 0 08 mEq /L as the A V difference This recovered level in A V difference was maintained thereafter In group II the initial value of 0 08 ± 0 04 mEq /L significantly changed to −0 23 ± 0 06 mEq /L after 7.5 minutes of occlusion and to −0 24 ± 0 06 mEq / L after 15 minutes of occlusion Rapid recovery to the initial level was observed at 5 minutes after reperfusion showing 0 03 ± 0 05 mEq /L and was maintained thereafter In group III the initial mean A V difference was 0 16 ± 0 03 mEq /L This value was successively inverted to −0 14 ± 0 04 mEq /L −0 33 ± 0 07 mEq /L and −0 23 ± 0 05 mEq /L after 10 20 and 30 minutes of occlusion respectively Even in this group rapid recovery to the initial level was observed at 5 minutes of reperfusion (0 11 ± 0 07 mEq /L)

In short among these three groups significantly elevated potassium concentration in venous

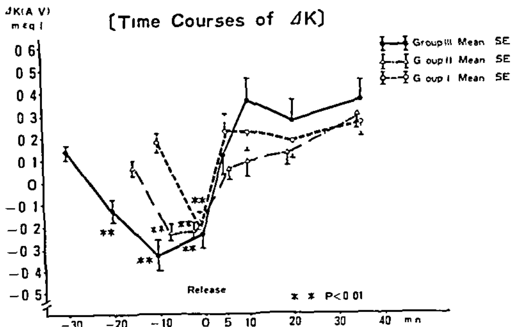


Fig 2 Time courses of ΔK (femoral artery great cardiac vein) are shown After occlusion ΔK was decreased. However immediately after reperfusion its recovery was observed in any group—I II and III

blood was detected during occlusion i e the venous K concentration was observed to exceed the arterial level Rapid recovery to the initial state was observed in every group on release of the occlusion

Summarizing all the results the time courses of ΔK recovered soon after reperfusion while changes in VMRT needed more time for recovery to the initial state Concerning heart rate serum pH and levels of Na Cl and Ca no significant changes were detected in the three groups

Discussion

Measurement of the ventricular fibrillation threshold was pioneered by Wiggers and Wegria[6,7] Although various methods[8] were subsequently developed each had both advantages and disadvantages We followed a modified Han s method as rapid assessment was required for the present study In this method defibrillation was not always necessary because in only a few cases did ventricular fibrillation occur spontaneously during experiments Many previous reports[1,2] have been concerned with the time courses of VFT or VMRT *during* coronary occlusion but there have been few reports[2] concerning VFT or VMRT after reperfusion following coronary occlusion Furthermore the effect of changing the duration of coronary occlusion on the time course of VFT or VMRT after reperfusion had never previously been studied Axelrod and associates reported that VFT (ventricular fibrillation threshold) was decreased for only a few minutes following reperfusion after 10 minutes of occlusion In agreement with their results our present study demonstrated that in the case of a 10 minute occlusion (group I) VMRT was decreased at 5 minutes after reperfusion but had recovered at 10 minutes after reperfusion Furthermore we studied the effect of the duration of occlusion time upon the VMRT time course after reperfusion Although only 10 minutes was required for the full recovery of VMRT in group I 20 minutes was required in group II and more than 40 minutes was required in group III

Since Harris and colleagues[13,14] pointed out that concentration of K was elevated in the adjacent coronary vein during occlusion and that K might play an important role in evoking ventricular arrhythmia we measured K in both the great cardiac vein and in femoral artery Concentration of K in the great cardiac vein was elevated by occlusion however it decreased rapidly to the initial level in every case of group I II and III The most likely explanation for the

mechanisms of release arrhythmia is the chemical and/or electrical gradients caused by washout metabolites and/or electrolytes that have accumulated in the ischemic area Lang and coworkers[15] pointed out that K in the great cardiac vein exceeded that in the aorta during coronary occlusion and it continued to do so even after reperfusion However our present study did not show persistent elevation of K after reperfusion A possible explanation of these differences is that Lang and associates[1] occluded the coronary artery for 3 hours in this time irreversible changes might occur in myocardial cells of the ischemic region therefore after reperfusion K loss might be persistent Jennings and colleagues[16] observed the reperfusion of the coronary artery following 20 minutes of occlusion ventricular fibrillation occurred more frequently than in the case of the reperfusion following 5 minutes of occlusion or following over 40 minutes of occlusion

Our present data demonstrated that there was no significant relation between the time courses of VMRT and those of the A V differences of K K might play an important role in arrhythmia during coronary occlusion but might not do so in arrhythmia after coronary reperfusion

Consequently the duration of the preceding ischemia resulting from coronary occlusion was relevant to the time courses of recovery of VMRT In other words the time courses of recovery in VMRT were dependent upon the duration of coronary occlusion time A possible explanation for these results may be that the longer the duration of the preceding occlusion time the more severe would be the myocardial damage due to myocardial ischemia

Summary

There have been many reports about ventricular arrhythmias during acute coronary occlusion Nevertheless it is only recently that interest has been taken in the occurrence of ventricular arrhythmia after reperfusion following coronary occlusion To investigate the mechanism of the latter kind of arrhythmia we studied the effect of changing the duration of occlusion time on the recovery time courses of the VMRT (Ventricular Multiple Response Threshold) and of the A V differences in the serum K concentration across the heart

The time course of ΔK recovered soon after reperfusion while changes in VMRT needed more time for recovery to the initial state Concerning heart rate blood pH and the levels of Na Cl and Ca no significant changes were detected There was no relation between the time courses of VMRT and those of the A V differences in serum K Consequently time courses in VMRT were dependent upon the duration of coronary occlusion time A possible explanation for these results may be that the longer the duration of the preceding occlusion time the more severe the myocardial damage due to myocardial ischemia

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Increased ejection fraction produced by a long-term subhypertensive infusion of norepinephrine in the conscious dog

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Previous studies on the hemodynamic effects of intravenous infusions of norepinephrine (NE) consisted of the administration of large doses of NE during a short period of time[1] These high doses of NE produced an increased arterial blood pressure an increased systemic peripheral resistance a reflex sinus bradycardia and a vari able effect on cardiac output NE initiated these hemodynamic changes by stimulating the alpha adrenergic receptors causing systemic vasocon striction and baroreceptor mediated reflex brady cardia[1-6] In contrast in a previous study we demonstrated that NE infused as a low (1 mcg / minute) acute subhypertensive dose produced systemic arteriolar vasodilatation and sinus *tachycardia* these hemodynamic effects have been postulated to be mediated through the beta adrenergic receptors in the systemic arteri *oles and* the sinus node In addition we have demonstrated that the infusion of norepinephrine chronically at a dose which did not increase the *systemic* pressure and did not change the heart rate resulted in ventricular hypertrophy Pre vious studies have demonstrated that a pressure overload produced ventricular hypertrophy re sults in a decreased ventricular function while a volume overload produced ventricular hypertro phy did not alter ventricular function[9] The purpose of this study was to determine the func tion of the ventricle resulting from a chronic subhypertensive infusion of norepinephrine in the conscious dog In order to avoid the alterations in ventricular function introduced by the trauma of open chest surgery and anesthesia a method was devised to instrument the cardiovascular system of dogs without requiring a thoracotomy and to study all the hemodynamic responses in the conscious dog[10]

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Methods

Five mongrel dogs weighing between 24 and 30 kilograms were anesthetized with 27 mg /kg of sodium pentobarbital First a polyvinyl chloride catheter of Tygon (/₁₆ in I D ⅛ in O D and 90 cm in length) was positioned in the mid thoracic aorta via the carotid artery Second a modified Cordis catheter No 521 842 was positioned in the left atrium across the intra atrial septum via the jugular vein[10] A third catheter was positioned in the right atrium using the same jugular vein All catheters were placed under fluoroscopic observa tion The catheter ends were subcutaneously tunneled and externalized through a stab wound and were then housed in a specially designed dog jacket[11] The catheters were heparinized (40 μ/ ml) twice a week[11]

The dogs were allowed a 10 day recovery period During this time in order to accommo date to the experimental apparatus they were placed in a modified Pavlov sling for light restraint Pressures and heart rates were recorded three times a week throughout the entire experi mental period In order to record cineangiograms

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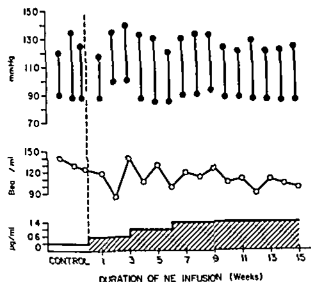


Fig 1 The effect of chronic norepinephrine infusion on aortic pressure and heart rate determined in a conscious dog Note the aortic blood pressure and heart rate are within the range of normal conscious dogs

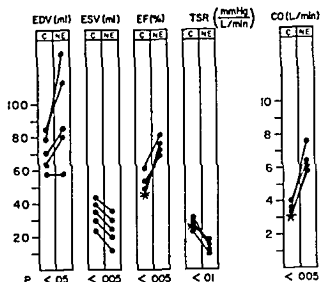


Fig 2 Hemodynamic effects of chronic infusion of norepinephrine (*NE*) in conscious dogs. *represents* hemodynamic data falling on the same points from two different dogs Observe that end-diastolic volumes (*EDV*) ejection fractions (*EF*) and cardiac outputs (*CO*) increased significantly while end-systolic volumes (*ESV*) and total systemic resistences (*TSR*) decreased significantly after NE infusion

the dogs were placed in the left lateral position and 30 ml of contrast material was pressure injected (100 p.s.i.) through the Cordis catheter into the left atrium Aortic pressure and a standard Lead II ECG were recorded simultaneously before during and after the cineangiogram No tranquilizers or sedatives were used The dogs remained calm throughout the procedure because they were frequently petted and spoken to in a soft voice

Using the formula for single plane cineangiography end diastolic volume (EDV) and end systolic volume (ESV) were determined from which stroke volume (SV) and ejection fraction (EF) were calculated After the cineangiogram was performed in the conscious dog the right atrial catheter was connected to a battery operated Sage microinfusion pump (No 216) The pump was set to deliver 2 ml per day The initial dose of NE was 0 5 mcg per minute (Fig 1) Dogs were maintained at this dosage for 2 weeks and then the dosage was increased to 0 9 mcg per minute After two more weeks the dose was increased to 1 4 mcg per minute and this dose was maintained throughout the remaining study period We have demonstrated that this incremental dose of NE does not increase the systemic arterial pressure in the conscious dog (Fig 1) NE maintains its potency within the infusion pump attached to the dog for a period of at least one week as demonstrated by NE dose response studies in our laboratory Dilution of NE was made with normal saline solution Pumps were refilled twice a week After each increase in the NE dose pressures and heart rates were monitored daily After 3 months of continuous infusion cineangiograms were repeated All cineangiograms were performed 20 to 30 minutes after stopping the infusion of NE Of importance is the fact that this animal preparation with a self contained infusion pump in a specially designed dog jacket' allows the animals to be free roaming in their cages

Results

In comparison with the control (values before infusion) 3 months of NE infusion resulted in an increase in stroke volume from 38 ± 3 3* to 67 ± 8 0 ml (p < 01) an increase in end diastolic volume from 72 ± 6 4 to 89 ± 12 9 ml (P < 05) and an increase in ejection fraction from 52 ± 3 6 to 76 ± 3 6% (P < 005) (Fig 2) Both heart rates and aortic pressures did not change significantly from the control heart rate was 100 ± 11 before and 103 ± 11 beats/minute after NE infusion (P > 05) and aortic pressure was 120/

*Mean ± SEM

88 ± 7/5 before and 129/84 ± 9/5 mm Hg after NE infusion (P > 05)

Discussion

In our laboratory we have developed a conscious dog preparation for long term infusion of NE an advantage of this preparation is that it does not have the hemodynamic variability introduced by anesthesia and thoracotomy Our current study on the effects of long term infusion of NE on hemodynamics utilizes this conscious dog preparation Our investigation differs from others because it has been limited to the nonhypertensive effects of NE thus we have maintained constant the important hemodynamic variable of systolic arterial pressure In our experimental design systolic arterial pressure was maintained at control levels because we utilized a pump in which the rate of infusion can be varied

NE is known to have a marked effect upon cardiac function by increasing cardiac chronotropy through a stimulation of cardiac beta adrenergic receptors Consistent with the concept of NE s chronotropic action on the heart were the results of our NE low dose hemodynamic response study in the conscious dog In that study an acute subhypertensive infusion of NE caused an increase in heart rate presumably by stimulating the cardiac beta receptors However our current study on the effects of continuous chronic subhypertensive NE infusion did not show an increase in the average heart rates over the period of infusion In the chronic NE infusion study the initial dose of 0 5 mcg /minute was below the level that was demonstrated to increase heart rate However the subsequent two week incremental doses of NE were sufficiently high to have increased the heart rate if administered acutely Therefore we postulate that chronic NE infusion decreases the sensitivity of the sinoatrial node to NE

The increased left ventricular ejection fraction produced by a long term infusion of NE is indicative of an increased inotropy the possibility that the increase in injection fraction is due to a decrease in systemic resistance cannot be eliminated Since the cineangiograms from which the ejection fraction were determined were performed 20 to 30 minutes after stopping the norepinephrine infusion the infused NE cannot be considered to be the direct [illegible] for the increased ejection fraction since infused NE is inactivated in less than 3 minutes The following mechanisms are postulated to explain this increase in inotropy (1) an increased sensitivity of the inotropic receptor, possibly the beta receptor (2) an increase in the size of the myocardial cells-myocardial hypertrophy and (3) an augmentation of the activity of the biochemical contractile machinery Firstly the possibility that the long term infusion of NE resulted in an increased sensitivity of the NE receptor to normal circulating NE is probably untenable In order to support this first possibility the inotropic and chronotropic beta receptors must have a markedly different threshold of response to explain the observed increase in contractility without concurrent increases in heart rate Probably a greater reason to reject the increased receptor sensitivity hypothesis evolves from our experience of chronic infusion of norepinephrine in the conscious dog After a chronic (4 weeks) increasing NE infusion to a level of 1 4 mcg /minute the BP and HR did not increase In contrast an acute infusion of 1 0 mcg /minute of NE caused both an increase in BP and HR Norepinephrine produced what is frequently observed with drugs a decrease not an increase in sensitivity after multiple doses Hypertrophy of the myocardium may certainly be considered a logical cause of increase in inotropy because the addition of more force producing contractile unit sarcomeres should increase ventricular function We have demonstrated that long term subhypertensive infusion of NE produces an increase in cardiac weight an index of myocardial hypertrophy however the results of previous studies on the effects of myocardial hypertrophy on contractility are conflicting In recent years several experimental[13 14] and clinical[1 1] studies have demonstrated that the myocardial hypertrophy consequent to pressure overload is associated with an impaired inotropic state However in the case of a volume overload induced hypertrophy indices of contractility have been demonstrated to decrease or not change [1] We consider that the reasons previous investigators have not been able to demonstrate an increase in ventricular function of the hypertrophied heart is that their experimental methods used created a load to the ventricle which was severe in magnitude and rapid in onset In addition the technique previously utilized may have altered ventricular function because both a

thoracotomy and pericardiectomy were performed Consequently we have chosen to utilize the term physiological myocardial hypertrophy for conditions in which the ventricular function increases in proportion to the increase in the myocardial muscle mass and the term pathological hypertrophy for the conditions of decreased ventricular function [9] Since chronic norepinephrine infusion produced an increase in ventricular weight we consider that myocardial cellular hypertrophy occurred and do not have to postulate an increase in biochemical contractile machinery Consequently we conclude that the myocardial hypertrophy produced by the NE infusion may be the explanation for the increase in ventricular function and therefore NE produced physiological hypertrophy

Summary

Five mongrel dogs with chronically implanted catheters in the left atrium mid thoracic aorta and right atrium were continuously infused with subhypertensive doses of norepinephrine for 3 months Left ventricular cineangiography determinations of aortic pressure and cardiac output were performed in the conscious dog After 3 months of continuous norepinephrine infusion stroke volume increased from 38 ± 3 0 to 67 ± 8 0 ml (p < 01) the left ventricular end diastolic volume increased from 72 ± 6 4 to 89 ± 12 9 ml (p < 05) and the ejection fraction increased from 52 ± 3 6 to 76 ± 3 6% (p < 005) We postulate that norepinephrine results in an increased myocardial function by producing physiological myocardial hypertrophy

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Dynamic electrocardiographic recording during sexual activity in recent post-myocardial infarction and revascularization patients

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Sexual activity in the cardiac (post myocardial infarction [post MI] and post myocardial revascularization [post MR]) patient continues to be of concern to patients, spouses, and physicians. Various authors[1] have related pertinent data regarding this subject; however, overall information and clinical research leading to definitive conclusions remains limited. The classification of coitus as benign in the cardiac patient has been recently questioned as a result of ambulatory monitoring in a physically conditioned post myocardial infarction patient. This particular subject was active in a medically supervised exercise program. He had ventricular ectopy identified during coitus on a 24 hour dynamic electrocardiographic recording (DER) and subsequently experienced reversible ventricular fibrillation while participating in the medically supervised program. Because of this observation, we questioned the significance of ventricular ectopy during coitus in the cardiac patient and to further investigate the problem, the study herein described was undertaken.

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Materials and methods

A randomly selected group of stable, uncomplicated post MI and post MR patients incorporated in an inpatient cardiac rehabilitation program were requested to return to the hospital for follow up evaluation at approximately two weeks after hospital discharge. All patients were asked if they were currently engaging in sexual activity. Those responding positively were submitted to a 24 hour dynamic electrocardiographic recording and were asked to participate in sexual activity during the 24 hour period of recording. The recorder was returned to the hospital on the following day. The tape was scanned utilizing an Avionics 660A Dynamic Electrocardioscanner and was referred to two cardiologists for final interpretation. In addition, 40 consecutive minutes of "real time" was recorded to include equal periods of time before and after sexual activity. This 40 minute strip was then analyzed for heart rate and dysrhythmias. The heart rate was calculated every minute utilizing a "heart rate ruler" for consistent accuracy.

The patient population was composed of nine post MI and 15 post MR patients. Although these are not comparable groups, the data are considered together since both have the same underlying disease process, i.e., coronary atherosclerosis. The nine post MI patients were all males with an age range of 37 to 66 ($\bar{X}$ 50.8) years. The infarction localization included five inferior, three anterior, and one subendocardial. The MR patients consisted of 12 males and three females with an age range of 39 to 57 ($\bar{X}$ 48.4) years. There was one non-white MR patient. In all cases the indication for surgery was angina pectoris which

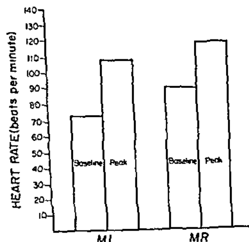


Fig 1 Comparison of baseline to peak heart rate during coitus of post MI and post MR patients

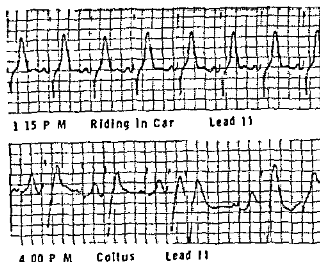


Fig 2 Comparison of DER during daily activities of a patient while riding in a car (normal sinus rhythm) and coitus (ventricular bigeminy and paired ventricular beats)

could not be well controlled by medical therapy The number of aortocoronary grafts per patient ranged from one to five with a mean of 3 2 Six of the MR group had previous myocardial infarctions and four of these occurred within three months prior to surgery The operative course in all cases was uneventful and the postoperative recovery was uncomplicated The time lapse from cardiac event to date of DER ranged from 21 to 38 days ($\bar{x}$ 30 1) in the post MI group and 20 to 38 days ($\bar{x}$ 31 5) in the MR group

This was the first sexual activity since cardiac event for ten of the total 24 patients None of the patients had associated diseases Medications and other clinical data are itemized in Table I

Results

Heart rate was calculated from a baseline resting rate to peak heart rate with sexual activity This resting baseline range in the post MI group was from 56 to 98 ($\bar{x}$ 74 0) beats per minute (BPM) with peak rate range from 86 to 150 ($\bar{x}$ 107 8) BPM The resting baseline range for the post MR patients was 72 to 106 ($\bar{x}$ 90 2) BPM with peak rate range from 92 to 156 ($\bar{x}$ 117 8) BPM (Fig 1) Total time for the heart rate to peak and return to baseline during sexual activity was calculated for each group (This was considered as total time for sexual activity) Total time for sexual activity ranged from 10 to 24 minutes ($\bar{x}$ 18 6) for the MI group and from seven to 35 minutes ($\bar{x}$ 18 8) for the MR group

Three of the nine post MI patients and nine of the 15 post MR patients had dysrhythmias during sexual activity (12 of the total 24) Of the three MI patients one had occasional premature ventricular contractions (PVCs) ($\leqq$ six isolated PVC/minute) with sexual activity as well as throughout the 24 hour period The second had rather constant ventricular bigeminy and ventricular coupling noted only during the ten minute period of coitus (Fig 2) and the third patient had an occasional premature atrial contraction (PAC) noted during coitus

Of the nine MR patients having abnormalities recorded during sexual activity five had occasional PVCs which were also noted at other times during the 24 hours One of these five experienced sexual activity twice during the 24 hour period and with a different partner for each episode The noon coitus was with his girl friend and a heart rate range of 96 to 150 BPM with occasional PVCs was noted During the evening coitus with his wife normal sinus rhythm with a rate range of 72 to 92 BPM was recorded Occasional PVCs were inscribed at other times during the recording The remaining four of the nine MR patients with sexual activity abnormalities had these recorded either with sexual activity only or more frequently with sexual activity (none of these four had infarction within three months prior to surgery) One had occasional PVCs noted as occurring more frequently during sexual activity than at other times (up to five in a 15 second

Table I Clinical data on 24 patients having dynamic electrocardiographic recording with sexual activity either post infarction or post revascularization

Patient	Age (years)	Sex	Race	Infarction location	Drugs	Days MI to DER	HR with SA		Dysrhy With SA	Dysrhy at other times
							Rest	Peak		
Infarction Group										
1	46	M	W	Anterior	Glyceryl trinitrate	28	62	100	1 PVC	Same
2	49	M	W	Subendocardial	Procainamide Propranolol	38	93	116	None	None
3	46	M	W	Inferior posterior	Isosorbide dinitrate	34	84	90	None	Occ PVCs
4	51	M	W	Inferior	Glyceryl trinitrate	36	86	150	None	Occ PVCs PACs
5	65	M	W	Antero lateral	Glyceryl trinitrate Warfarin sodium Isosorbide dinitrate Diazepam	30	68	90	None	Occ PVCs
6	37	M	W	Infero posterior	Chlordiazepoxide Procainamide	21	58	86	None	Same
7	49	M	W	Infero posterior	None	34	56	136	Vent bigeminy Vent coupling Frequent PVCs	Occ PVCs
8	54	M	W	Inferior	Procainamide	24	82	102	Occ PACs	None
9	38	M	W	Antero lateral	Insulin Propranolol Isosorbide dinitrate	26	72	100	None	None

Abbreviations M = male F = female DER = dynamic electrocardiographic recording HR = heart rate in beats per minute No = number PVC = premature ventricular contraction Vent = ventricular PAC = premature atrial contraction B = black Occ = occasional Tach tachycardia (C) = girlfriend (W) = wife WPW = Wolff Parkinson White pattern (1) and ( ) in patient No 6 and 9 data = first (1) and second ( ) sexual act of the 24 hour period Dysrhy = dysrhythmias MI = myocardial infarction SA = sexual activity

period) Another had occasional PVCs pairs of ventricular extrasystoles and an episode of chaotic atrial tachycardia at a rate of 135 BPM during sexual activity The PVCs PACs and paired ventricular extrasystoles were recorded at other times on the monitor but chaotic atrial tachycardia was recorded only with sexual activity The other two MR patients experienced sexual activity twice within the 24 hour period One of these demonstrated frequent PVCs in addition to two consecutive ventricular beats (probably re entry) during his evening coitus (Fig 3) but no arrhythmias during his morning coitus Only occasional PVCs were recorded during the remaining portion of the 24 hours The other patient demonstrated an almost constant Wolff Parkinson White (WPW) syndrome pattern throughout sexual stimu[illegible]n in both the morning and evening episode[illegible]th only intermittent WPW during the other p[illegible]on of the record (Fig 4) This patient (a wid[illegible]tilized a mechanical vibrator for stimulati[illegible]

Of the total of 12 patients (50 per cent) experiencing abnormalities during sexual activity (nine post MR and three post MI) five (one MI and four MR a total of 20 per cent) were considered to have more serious changes than the other seven MR and MI patients demonstrating occasional PVCs or PACs These more serious changes were defined as frequent PVCs or PACs These more serious changes were defined as frequent PVCs (five PVCs in a 15 second period) paired PVCs ventricular bigeminy and a constant WPW pattern

Discussion

The data presented support in part those previously documented by Hellerstein and Friedman In the analysis of coitus in 14 post coronary patients they found a mean heart rate of 117.4 BPM with an average duration of intercourse of 16.3 minutes This time interval was calculated between retiring to bed and attainment of maximal heart rate associated with coitus Three of

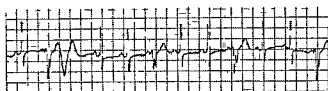
Table I continued

Patient	Age (years)	Sex	Race	No bypass grafts	Drugs	Days Surg to DER	H R with S A Rest	H R with S A Peak	Dysrhy with S A	Dysrhy at other times
Revascularization Group										
1	53	M	W	5	Aspirin	36	106	144	None	Occ PVCs
2	46	M	W	3	Aspirin	31	100	[illegible]	One fusion beat	Occ PVCs
3	43	M	W	4	Procainamide	31	82	122	Occ PVC PAC	Occ PVC
4	51	M	W	1	Aspirin	33	72	96	None	Occ PVCs
5	53	M	W	5	Lanoxin Hydrochlorothiazide	35	100	120	Occ PVCs Chaotic atrial vent coup tach. (135/min) Vent Couplet	Vent Coup Occ PVCs
6	44	M	W	3	Percodan (Oxycodone)	29	(1) 86	116	(1) Freq PVCs Vent couplet	Occ PVCs
							(2) 82	106	(2) None	
7	39	M	W	1	Aspirin	21	80	156	None	None
8	51	F	W	1	Flurazepam Acetaminophen	31	78	92	None	None
9	53	F	W	1	Glyceryl trinitrate Acetaminophen	[illegible]	(1) 104	116	(1) WPW with vibrator	Intermittent WPW
							(2) 102	130	(2) WPW with vibrator	
10	46	M	B	5 (3/23/77) 3 (9/22/77)	Aspirin	28	(G) 96	150	(G) Occ PVCs	Occ PVCs
							(W) 72	92	(W) None	
11	49	M	W	3	None	38	95	140	Occ PVC	Occ PVCs
12	50	M	W	5	Percodan (Oxycodone)	20	98	116	Occ PVCs	Occ PVCs
13	57	M	W	2	Aspirin Lanoxin	36	100	100	None	Occ PVCs
14	43	M	W	3	Quinidine gluconate Triamterene hydrochlorothiazide	34	74	94	None	None
15	53	F	W	3	Acetaminophen hydrochlorothiazide	38	96	110	Frequent PVCs	Occ PVCs

the 14 subjects developed ectopic beats Two of these had ventricular ectopy and one had both atrial and ventricular ectopy When comparing electrocardiographic reponse during coitus to other times during the day they concluded that the cardiovascular response was similar during coitus and usual occupational activities In comparison the data reported herein describe an average peak heart rate of 107 8 for MI patients and 117 8 for MR patients with a duration of sexual activity of 18 6 minutes (MI) and 18 8 minutes (MR) In contrast to three of 14 subjects experiencing dysrhythmias with sexual activity in previous reports the data herein reveals that 12 of 24 patients developed abnormalities (three of nine MI patients and nine of 15 MR patients)

When eliminating occasional PVCs and PACs five of 24 patients (one MI and four MR) had abnormalities either with sexual activity only or more frequently with sexual activity These changes were not seen during other portions of the 24 hour recording when daily activities included such chores as bathing shaving dressing cooking putting groceries in pantry and other light housework or when exercise activities included one or two flights of stair climbing or walking less than one half mile at a leisurely pace

When considering the difference in yield of abnormalities with sexual activity between the data presented here and that reported elsewhere one must consider the time of data collection in



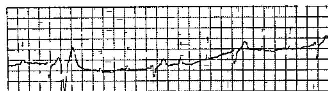
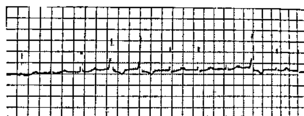


Fig 3 DER *(Lead II and Lead CM_5)* during evening coitus in a post MR patient showing frequent PVCs and two consecutive ventricular beats (probably re entry)



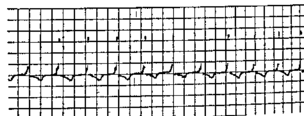


Fig 4 Comparison of DER during daily activities of a patient while walking (intermittent WPW) and sexual activity (constant WPW)

relation to the cardiac event Hellerstein and Friedman s patients were post coronary patients already participating in an outpatient exercise program Our patients in contrast were studied earlier a mean time of 30 1 days post MI and 31 5 days post MR

Stein[1] has shown an increase in aerobic capacity and a reduction in peak coital heart rate from 127 BPM to 120 BPM in trained post myocardial infarction patients These patients had experienced a 16 week bicycle ergometer training program at 12 to 15 weeks following their first myocardial infarction The author did not discuss dysrhythmias and it would be interesting to know the training effect on the presence or incidence of dysrhythmias with coitus

The data herein presented relate a notable degree of cardiac electrical instability recorded with sexual activity in 12 of 24 patients (50 per cent) Of the total of 12 five had abnormalities only with or notably more with sexual activity as compared to other times on the 24 hour record More MR patients had abnormalities than MI patients (nine of 15 versus three of nine) and there was also a slightly higher peak heart rate in this group compared to the MI group Considering the number of higher grade dysrhythmias there were no early fatalities in this group of 24 patients However there may be some cause for concern regarding the ultimate long term prognosis as current data suggest a higher incidence of sudden death associated with such degrees of ventricular ectopy

Based on the data in this group of subjects it is therefore felt that sexual activity in recent post MI and post MR patients may be a stimulus for cardiac electrical instability In accord with this appropriate concern should be expressed in patient management and counseling and consideration should be given to the use of antidysrhythmic drugs

Summary

Twenty four post cardiac patients had 24 hour DER at a mean time of 30 1 days post MI and 31 5 days post MR All patients experienced sexual activity at least once during the 24 hours Heart rate ranged from a mean of 74 0 to 107 8 BPM in the MI group and from 90 2 to 117 8 in the MR group Sexual activity duration averaged 18 6 minutes in the MI group and 18 8 minutes in the MR group Twelve of the 24 patients recorded cardiac electrical abnormalities during sexual activity and five of these 12 had abnormalities associated only with or more frequently with sexual activity It is concluded that sexual activity may provoke cardiac electrical events not elicited by other stimuli and this may warrant consideration for patient counseling and/or specific therapy

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The influence of left ventricular filling pressure on atrial contribution to cardiac output

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The significance of atrial contraction in ventricular filling was appreciated as early as 1628 by William Harvey, who described pulsatile blood flow from atrium to ventricle in the frog heart Subsequent studies have quantified the importance of atrial contribution to ventricular performance in both animal models [6] and in patients [12] In subjects with normal ventricular function and appropriately timed atrial contraction appears to increase cardiac output significantly [7,11] It has been postulated that atrial contribution plays a more important role in maintaining cardiac output in the failing than in the non failing heart [11] Although this concept has been widely accepted supporting evidence is not conclusive

Patients with left ventricular failure usually have elevated end diastolic pressures Since a curvilinear relationship between a stroke volume and end-diastolic pressure is described by the ventricular function curve [13] the level of end diastolic pressure would be expected to influence atrial contribution [1] When end diastolic pressure is in the normal range the left ventricular function curve is steepest and the atrial contribution should increase stroke volume maximally When end diastolic pressure is elevated the flat portion of the ventricular function curve is approached and further increments in pressure would be expected to have progressively less effect in augmenting stroke volume

The purpose of this study was to determine what influence left ventricular filling pressure might have on the atrial contribution to cardiac output

Methods

A Patient population Hemodynamic studies were performed in 18 patients described in Table I There were 15 males and three females their ages ranged from 18 to 73 years with a mean of 54 years Cardiac disease was attributed to coronary artery disease in 10 patients (Table I patients No 1 3 9 to 11 13 to 16 18) aortic valve disease in five patients (Table I patients No 2 4 5 7 8) and to other causes in three patients (Table I patients 6 12 17) A history and physical findings consistent with congestive heart failure was present in five patients (Table I patients 14 to 18) Ventricular function was evaluated by angiography just prior to surgery in the postoperative patients and immediately prior to study in all other patients An ejection fraction of less than 50 per cent by either contrast angiography [11] or radionuclear angiography [1] was considered evidence of abnormal left ventricular function Ten patients were studied within 24 to 48 hours of open heart surgery (coronary artery bypass in

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Table I Clinical information and summary of results

Patient	Age	Sex	Diagnosis	Studied	Intervention	Atrial pacing					Ventricular pacing					Atrial Contribution cc/M
						HR	$\overline{BP}$ mm Hg	$\overline{PAP}$ mm Hg	$\overline{PCW}$ mm Hg	SVI cc/M	HR	$\overline{BP}$ mm Hg	$\overline{PAP}$ mm Hg	$\overline{PCW}$ mm Hg	SVI cc/M²	
1	55	M	CAD	Post-op	Baseline	102	86	17	12	36	102	80	27	17	30	6
					Fluid	102	94	28	24	45	102	90	36	30	35	10
2	70	M	AS	Post-op	Baseline	88	76	17	10	35	88	70	22	13	26	9
					Fluid	88	82	28	22	40	88	80	32	25	31	9
3	51	M	CAD	Post op	Baseline	100	116	28	17	35	100	114	32	23	28	7
					Fluid	100	122	31	22	32	100	130	34	–	24	8
4	18	M	AS	Post-op	Baseline	96	88	10	8	45	96	86	15	10	34	11
					Fluid	102	96	18	11	61	102	94	20	13	47	14
					Fluid	102	94	25	18	66	102	98	25	24	55	11
5	61	M	AI	Post-op	Baseline	90	92	19	8	51	90	85	19	12	30	21
					Fluid	90	91	35	17	65	90	90	42	20	44	21
6	41	M	ASD	Post op	Baseline	83	82	22	1	42	83	76	18	18	36	6
					Fluid	83	84	32	23	42	83	86	28	23	39	3
					Fluid	83	86	37	28	46	83	84	34	27	39	7
7	51	M	AS	Post op	Baseline	92	80	1	12	38	92	64	23	17	29	9
					Fluid	98	90	23	23	42	98	86	34	25	34	8
8	64	M	AS	Post-op	Baseline	104	82	26	18	40	104	80	28	26	27	13
9	54	M	CAD	Post-op	Baseline	95	84	32	19	44	95	80	36	19	35	9
					Fluid	95	84	34	29	45	95	96	38	31	45	0
					Isordil	96	76	24	20	42	96	66	30	20	32	10
10	73	F	CAD	Post-op	Baseline	84	85	34	20	31	84	98	32	20	30	1
					Isordil	84	83	22	15	34	84	86	26	15	26	8
11	38	M	CAD	At cath	Baseline	100	99	15	10	26	100	92	23	19	20	6
12	42	M	Normal	At cath	Baseline	109	–	20	9	33	109	–	25	10	29	4
13	55	M	CAD	At cath	Baseline	92	–	21	16	34	92	–	26	20	24	10
14	74	F	CAD/HP/CHF	At cath	Baseline	107	120	30	22	15	107	116	28	21	13	2
					Fluid	107	131	34	28	21	107	105	28	25	18	3
15	51	M	CAD/HP/CHF	At cath	Baseline	109	140	55	25	18	109	130	43	28	20	0
16	59	M	CAD/CHF	CCU	Baseline	80	74	33	25	31	80	68	34	23	25	6
					Isordil	80	75	25	18	33	80	68	27	17	26	7
17	50	F	MR/CHF	CCU	Baseline	100	127	47	33	21	100	115	47	33	17	4
					Isordil	100	113	36	27	24	100	109	43	28	20	4
					Isordil	105	113	37	25	18	105	100	37	28	16	2
18	57	M	CAD/CHF	CCU	Baseline	98	107	44	33	20	98	93	43	35	17	3
					Isordil	109	–	32	26	21	109	103	31	23	15	2

Abbreviations HR = heart rate $\overline{BP}$ = blood pressure $\overline{PAP}$ = pulmonary artery pressure mean $\overline{PCW}$ = pulmonary capillary wedge mean SVI = stroke volume index CAD = coronary artery disease AS = aortic stenosis AI = aortic insufficiency ASD = atrial septal defect CHF = congestive heart failure HP = hypertension MR = mitral regurgitation.

four aortic valve replacement in five and repair of atrial septal defect in one) Perioperative infarction was evaluated by new Q waves on electrocardiogram and by technetium 99m pyrophosphate myocardial imaging Recent infarction was diagnosed in only one patient Five patients were studied at the time of diagnostic cardiac catheterization Three patients admitted to the Coronary Care Unit for therapy of congestive heart failure were studied prior to the initia

Table II Comparison of hemodynamics and cardiac output during atrial and ventricular pacing

	Number	Heart rate	$\overline{BP}$ mm Hg	$\overline{PA}$ mm Hg	$\overline{PCW}$ mm Hg	$\overline{RA}$ mm Hg	SVI cc/M
Atrial	35	95 8	95 4	27 8	19 7	11 7	36 3
Ventricular	35	95 8	91 5	30 9	22 9	13 4	?9 0

tion of any new therapeutic protocol All patients were clinically stable Patients were continued on their usual medications however vasodilator drugs and diuretics were withheld until the completion of the study Informed consent was obtained from each patient

B Study protocol The atrial contribution to cardiac output was measured by comparing stroke volume during atrial and ventricular pacing at a constant heart rate Intermittent atrial contribution during ventricular pacing was avoided as described below The *absolute* atrial contribution was determined by the difference in stroke volume between atrial and ventricular pacing whereas the *relative* atrial contribution was measured as the absolute atrial contribution divided by the stroke volume during ventricular pacing and expressed as per cent After baseline measurement of the atrial contribution end diastolic pressure was either raised by volume expansion using normal saline or whole blood if clinically indicated (11 studies) and/or lowered by sublingual Isordil (six studies) in 13 patients and atrial contribution was again assessed

To determine whether asynchronous ventricular contraction during ventricular pacing adversely affected ventricular performance stroke volume during atrial pacing and atrioventricular (A V) sequential pacing at identical heart rates were compared in 17 patients at initial pulmonary capillary wedge pressures (PCW) Measurements were repeated following volume expansion (eight studies) and/or after the use of sublingual nitrates (two studies) in seven of these patients

C Pacing An American Optical bifocal pacing unit with adjustable PR interval was used All patients were in normal sinus rhythm and pacing was instituted at a rate approximately 10 beats/minute above the intrinsic heart rate Effective atrial systole during atrial pacing was documented by the appearance of the a wave in either the pulmonary capillary wedge or left ventricular end diastolic pressure tracing During A V sequential pacing the right atrium and right ventricle were stimulated separately and sequentially keeping the simulated PR interval shorter than the intrinsic P R interval To assure that ventricular depolarization was not caused by conduction along normal pathways during sequential pacing the P R interval was decreased until the QRS configuration and duration were identical to that seen during ventricular pacing During ventricular pacing both atrium and ventricle were stimulated separately but the simulated interval was decreased to 00 seconds so that atrial and ventricular systole coincided and atrial contribution was avoided If the atria and ventricles were not simultaneously depolarized intermittent atrial contribution was sometimes noted

In the 10 postoperative patients steel electrodes which had been sutured to the right atrial appendage and epicardial surface of the right ventricular free wall and indifferent electrodes which were attached subcutaneously over the abdomen were used to perform pacing studies Such electrodes are routinely placed in patients undergoing open heart surgery at this institution In five patients studied during catheterization bipolar pacing catheters were placed in the coronary sinus and right ventricular apex In the remaining three patients a Swan Ganz multipurpose catheter with both atrial and ventricular electrodes was used [1] Ventricular electrodes were positioned near the right ventricular apex

D Hemodynamic measurements In all studies pacing was maintained for at least two minutes before measurements of pressure and cardiac output were taken Right atrial (RA) pulmonary artery (PA) and pulmonary capillary wedge (PCW) pressures were recorded with a balloon tipped triple lumen catheter Cardiac output (CO) was measured by thermodilution techniques with the same catheter [1] Cardiac outputs were performed in triplicate with a variation of less than 10 per cent Cardiac output computations were performed by a bedside computer (Santa Barbara Technology Inc Model 1700) In seven patients left ventricular end diastolic pressure was measured through a

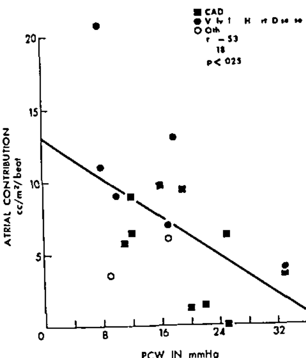


Fig 1 Influence of filling pressure on atrial contribution at baseline PCW A significant inverse relation hip between absolute atrial contribution and PCW is shown As PCW increases the atrial contribution tends to become less

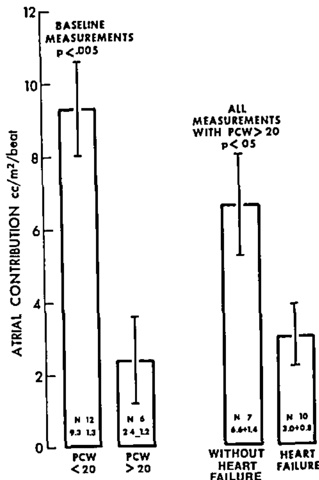


Fig 2 Evaluation of atrial contribution by initial PCW and by left ventricular performance in patients with elevated PCW *The first panel* assesses atrial contribution at baseline by dividing the population on the basis of a PCW either greater than or less than 20 mm Hg *The second panel* assesses atrial contribution in all studies performed at a PCW ≥ 20 mm Hg and includes measurements performed after volume loading and/or nitrates were used Studies were divided on the basis of a history of congestive heart failure Atrial contribution is significantly less in patients with a history of congestive failure (*PCW* = pulmonary capillary wed e pressure *vertical bars* = standard deviation)

number 8 French pigtail catheter Arterial blood pressure (BP) was obtained by cuff readings or by cannulation of the radial artery with a No 20 angiocath The mean arterial pressure ($\overline{BP}$) was estimated from the formula

$$\overline{BP} = D + \frac{(S - D)}{3}$$

while the mean systolic pressure ($\overline{SP}$) was esti mated as

$$\overline{SP} = D + \frac{2(S - D)}{3}$$

where S is the peak systolic and D the diastolic pressure

Derived hemodynamic parameters were calcu lated as follows Cardiac index (C I) = C O / body surface area (B S A) (L/min/M) Stroke volume index (S V I) = stroke volume (S V)/ BSA (ml/M) Stroke work index (S W I) = ($\overline{SP}$ − PCW) × SVI × 0136 (gm m / M)

Results

The measurement of pressures and cardiac output during atrial and ventricular pacing from 35 studies in 18 patients is shown in Tables I and II For all studies S V I was higher by an average of 25 per cent when the atrial contribution was present In Fig 1 the atrial contribution was plotted against baseline PCW pressure As PCW increased atrial contribution decreased ($r = -53$ $p < 025$) Since stroke volume tended to be lower in patients with elevated PCW the relative atrial contribution to stroke volume was also plotted against PCW A similar trend ($r = -41$ $p < 05$) was noted When patients

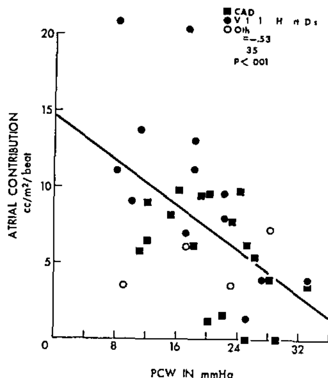


Fig 3 Influence of filling pressure on atrial contribution for all studies The studies represent measurements performed at baseline and after PCW had been modified by volume and/or nitrates A significant inverse relationship between absolute atrial contribution and PCW is shown

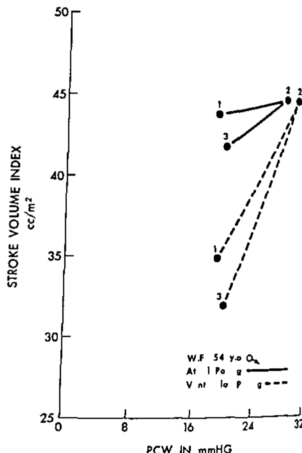


Fig 4 Influence of left ventricular filling pressure on atrial contribution in an individual patient Measurements were done (1) at baseline (2) after 300 c c whole blood and (3) after 15 mg sublingual isosorbide dinitrate

whose initial PCW was < 20 mm Hg (Table I patients 1 to 13) were compared to patients whose PCW was ≥ 20 mm Hg (Table I patients 14 to 18) atrial contribution was significantly greater in patients with lower PCW (9 3 ± 1 3 vs 2 4 ± 1 2 c c /M) as shown in Fig 2

Since all patients whose baseline PCW was ≥ 20 mm Hg had evidence of impaired ventricular function by history and angiography the influence of filling pressure on atrial contribution was again assessed after PCW had been modified by volume loading in patients with low PCW and following nitrates in patients with PCW ≥ 20 mm Hg In Fig 3 the atrial contribution in 35 studies (i e including measurements performed at initial PCW and following use of volume load and/or nitrates) was considered Atrial contribution again tended to decrease with increasing PCW (r = −53 p < 001) [illegible] ative atrial contribution showed a similar [illegible] (r − 44 p < 005) These data include [illegible] done after considerable change in [illegible] had been accomplished in several pa[illegible] determinations were performed in patients without a history of heart failure who had been volume loaded to PCW ≥ 20 mm Hg in Fig 4 shows the relationship between left ventricular filling pressure and atrial contribution in such a patient The study was done 24 hours following uncomplicated coronary bypass surgery at a time when the patient was clinically stable Preoperative left ventricular angiography had shown normal left ventricular function and there was no evidence of perioperative infarction Initially the PCW was 19 mm Hg and an atrial contribution of 27 per cent was noted (see No 1 Fig 4) After increasing PCW to 29 mm Hg no change in stroke volume was noted when pacing was changed from the atrial to the ventricular mode (see No 2 Fig 4) indicating that atrial contribution was ineffective in augmenting stroke volume at this level of PCW Following sublingual Isordil the PCW returned to baseline level and an atrial contribution of 30 per cent was seen (see No 3 Fig 4)

le III Comparison of hemodynamics and cardiac output during atrial and A V sequential pacing

	Number	PR sec	QRS sec	Heart rate	$\overline{BP}$ mm Hg	$\overline{PA}$ mm Hg	$\overline{PCW}$ mm. Hg	$\overline{RA}$ mm Hg	SVI cc/M
l	28	.22	08	100	97 4	27.3	17.2	10 1	32.1
sequential	28	13	13	100	95 4	28 6	17 6	10.5	32.3

nally the atrial contribution in patients with line PCW ≥ 20 mm Hg *was compared with* obtained in patients who had received a fluid to increase PCW ≥ 20 mm Hg PCW was roximately equal in both groups Patients baseline PCW ≥ 20 mm Hg all had a histo f congestive heart failure and all had evidence npaired ventricular function as evidenced by ejection fraction of < 55 per cent and a I < 35 gm m /M No patient who was ime loaded had a history of heart failure hough several patients in this group were lied postoperatively and conceivably may e had changes in left ventricular function all a SWI > 35 gm m /m² at baseline prior to d load As shown in the second panel of Fig 2 atrial contribution was significantly greater patients without a history of heart failure than those with a history of congestive failure ± 1 4 vs 3 0 ± 0 8 c c /M p < 05)

When hemodynamic measurements during ial and A V sequential pacing were compared re was little difference in pressures or cardiac tput despite an increase in QRS duration from to 13 sec during A V sequential pacing (Table) As shown in Fig 5 stroke volume was similar th atrial or A V sequential pacing in 28 studies cluding determinations at baseline and after ervention) in 17 patients

scussion

These data suggest that left ventricular filling essure *influences the atrial contribution to* oke volume As filling pressure increases the ial contribution tends to become less effective augmenting stroke volume Since the patients *th PCW ≥ 20 mm* Hg at baseline had evidence left ventricular dysfunction we considered the ssibility that atrial contribution might be rela vely more important despite the fact that the solute value was reduced since total stroke lume was lower When we evaluated the rela ve atrial contribution an inverse relationship between stroke volume and PCW similar to that *noted for the absolute value was seen When the* relationship between atrial contribution and PCW for all 35 studies (including those performed at baseline as well as after modification of PCW) was examined an inverse relationship which was highly significant (p < 001) was again noted This suggests that the tendency for the atrial contribution to diminish as PCW increased was not determined by a small group of patients with congestive heart failure since this analysis included data from patients who had no history of heart failure but whose PCW had been raised to above 20 mm Hg by fluid load The patient illustrated in Fig 4 exemplifies the effect that changes in left ventricular filling pressure may have on atrial contribution However it does appear as shown in the second panel of Fig 2 that when PCW is above 20 mm Hg *subjects* with impaired ventricular function derive signifi cantly less benefit from atrial contribution than *do subjects with normal left ventricular function* This finding raises the question of abnormal left atrial function in patients with impaired ventric *ular function which may also contribute to the* observed reduction in atrial contribution in this group of patients

Although a significant correlation was found there is considerable scatter of individual values around the regression line describing the relation ship of atrial contribution and PCW It is impor tant to point out that these data suggest a relationship between the atrial contribution and left ventricular filling pressure but they cannot be used to predict the magnitude of the atrial contribution in an individual patient The degree of variability between patients was not unex pected As described below *we attempt to explain* our findings by the Frank Starling mechanism and the left ventricular pressure–volume relation ship Since the curves used to describe these relationships may show considerable variability between individual patients

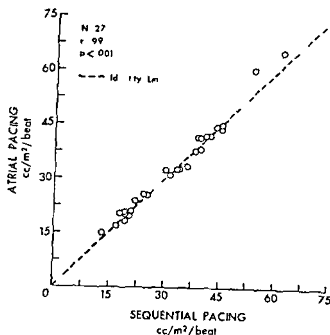


Fig 5 Comparison of stroke volume index during atnal and A V sequential pacing. In both instances the atnal contribu tion is present however during sequential pacing asynchro nous ventricular contraction occurs

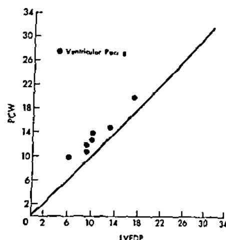


Fig 6 Relationship of LVEDP and PCW during ventricular pacing Pressures were obtained simultaneously during ventricular pacing A slight tendency for PCW to overestimate LVEDP is noted

that there is variability of the relationship of PCW and atnal contribution

In this study PCW was used to estimate left ventricular end diastolic pressure However PCW is more closely related to mean diastolic pressure rather than to end diastolic pressure[7] This is particularly true in patients with a prominent a wave In the six patients in whom simultaneous LVEDP and PCW were measured the mean difference was 1 2 mm Hg Conversely during ventricular pacing when simultaneous atnal and ventricular contraction causes retrograde propul sion of blood from the left atrium to the pulmo nary veins the PCW may overestimate true LVEDP As shown in Fig 6 when simultaneous PCW and LVEDP were measured during ventric ular pacing in seven patients the differences were again small Although PCW is only an estimate of true filling pressure it is unlikely that the trends encountered in these studies were significantly affected by using PCW rather than LVEDP

The reasons why the atnal contribution tends to diminish as left ventricular filling pressure is increased can be explained by two interrelated mechanisms As shown in Fig 7 the curvilinear shape of the left ventricular pressure–volume relationship predicts that when the steep portion of the curve is reached further increments in volume result in large increments in pressure[21] If the steep part of this curve is approached prior to atnal systole a large increase in pressure would accompany a further increase in volume This sharp rise in pressure would act to impede left ventricular filling thus reducing the atnal contri bution This effect would be particularly potent in cases where the left atnal pump was also failing In addition the shape of the left ventric ular function curve predicts that when the left ventricular diastolic pressure is elevated a fur ther increase in pressure (resulting from the atnal contribution) would be expected to have less effect in increasing stroke volume than it would when pressures are lower and the curve is steep er[13] In subjects with impaired left ventricular function the shape of this curve is flatter than in normals Consequently the increase in stroke volume that results from the atnal contribution would be even less in these subjects than in normals

Previous studies have not evaluated the influence of left ventricular filling pressure on atnal contribution Gillespie and associates[14] reported that atnal contribution was decreased in subjects with impaired ventricular function Several reports have suggested that atnal contri bution tends to play a greater role in increasing stroke volume in subjects with impaired left ventricular function than it does in normal subjects [17] However these reports did not

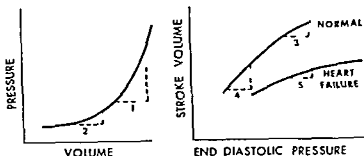


Fig 7 *Left panel* Left ventricular pressure–volume relationship *Right panel* Left ventricular function curve In subjects with elevated filling pressure increase in ventricular volume can be accomplished only by a large increase in pressure *(point 1)* at lower initial pressure a similar increase in volume is accommodated with much less rise in pressure *(point 2)* In addition the same increment in pressure in a subject with high end-diastolic pressure *(point 3)* results in less increase in stroke volume than would occur with lower end diastolic pressure *(point 4)* In heart failure this same increment in pressure might be expected to have even less of an effect on stroke volume *(point 5)* as the curve is flatter

evaluate the influence of left ventricular filling pressure on atrial contribution Rahimtoola and co workers [1] studied patients shortly after myocardial infarction and found that when the patients were divided by cardiac index those with reduced values had significantly higher atrial contribution despite higher left ventricular filling pressures The reason for the discrepancy between these studies is uncertain It is of interest that when Rahimtoola s population was divided on the basis of end diastolic volume the atrial contribution to the left ventricular end diastolic volume was considerably less in subjects with ventricular volumes greater than or equal to 110 c c /M than in subjects with smaller ventricles This can be interpreted as showing that these patients were now on the steep portion of the pressure–volume curve and further ventricular filling was poorly accomodated This would support our hypothesis DeMaria and co workers found that the atrial phase of ventricular filling was more important in subjects with CAD than in normals However left ventricular end diastolic pressure was normal or only slightly elevated in these patients and the influence of left ventricular filling pressure was not assessed

In order to determine whether the difference between atrial and ventricular pacing was due exclusively to the loss of atrial contribution or was in part determined by a deleterious effect of asynchronous contraction on ventricular performance stroke volumes during atrial and A V sequential pacing were compared In both instances atrial contribution was maintained During atrial pacing depolarization progressed along normal pathways while with A V sequential pacing asynchronous ventricular contraction occurred These data demonstrate that when the atrial contraction is maintained ventricular function is not adversely affected by asynchronous ventricular contraction Although studies in dogs have suggested that ventricular performance is adversely affected by asychronous contraction [2] Samet and colleagues[3] found no significant difference in stroke volume during asynchronous contraction in man Our results support the findings of Samet and associates and in addition suggest the pacing from either the epicardial surface of the right ventricular free wall or from the apex does not adversely affect ventricular performance Of note is the observation that shortening of the PR interval during sequential pacing did not alter stroke volume These findings are consistent with work by Ruskin and co workers which showed that stroke volume did not vary if the PR interval was kept in the range of 0 05 to 0 20 sec

These data show that atrial contribution results in considerable hemodynamic benefit in patients with normal filling pressure In addition if a properly timed atrial contraction is maintained asynchronous ventricular contraction does not have a deleterious effect on ventricular performance As filling pressure rises the atrial contribution tends to be of less importance although individual patients may vary considerably On the basis of these data the increment in stroke volume that results from the atrial contri

bution can be expected to be less in patients with heart failure than in patients with normal filling pressures

Summary

The influence of left ventricular filling pressure on the atrial contribution to cardiac output was evaluated in 18 patients An inverse relationship between filling pressure and atrial contribution was seen in studies done at baseline (PCW (r = −.53 p < .025) as well as in studies done after PCW was modified by volume expansion and/or nitrates (r = −.53 p < .005) At baseline atrial contribution averaged 9.3 ± 1.3 cc/M in patients with PCW < 20 mm Hg while it was only 2.4 ± 1.2 cc/M in patients with PCW ≥ 20 mm Hg (p < .005) Atrial contribution was significantly greater in patients who had no history of heart failure when they were volume loaded to a PCW above 20 mm Hg than in patients with impaired ventricular function whose baseline PCW was above 20 mm Hg Thus atrial contribution tends to be less effective in augmenting cardiac output when filling pressure is already elevated particularly in patients with impaired left ventricular function

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Value and limitations of technetium-99m stannous pyrophosphate in the detection of acute myocardial infarction*

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Hot spot myocardial imaging with technetium 99m stannous pyrophosphate (mTc PYP) has been proposed as a means of diagnosing acute myocardial infarction (AMI) and quantifying infarct size [1] This bone scanning agent concentrates maximally in the region of infarcted myocardium possibly by the binding of pyrophosphate to calcium which is deposited in the mitochondria of irreversibly damaged cells [1] [14] Myocardial uptake of mTc PYP requires sufficient residual regional blood flow for delivery of the tracer to the area of myocardial injury being maximal in the peripheral border zones of infarction with flows of 30 to 40% of normal and minimal in the central zones [1] [15] [16] Scintigrams tend to become positive within 12 hours after AMI and then fade six or seven days later

In addition to AMI positive mTc PYP scintigrams with uptake in the heart have been reported in approximately one third of patients with unstable angina in patients with ventricular aneurysm and old myocardial infarction and in conditions in which muscle necrosis is due to etiologies other than coronary artery disease including myocardial contusion [0] repeated cardioversion [21] metastatic tumors and cardiomyopathy

There are clinical circumstances where routine diagnostic techniques for AMI are not helpful and where the addition of an effective and sensitive test for myocardial necrosis would be of value These circumstances include (1) patients with a conduction disturbance or electrocardiographic (ECG) evidence of previous infarction that interferes with the demonstration of a new infarct pattern (2) patients who have a typical history of prolonged chest pain together with serial ST depression and T wave inversion and yet have normal enzyme determinations (3) patients who undergo coronary artery revascularization and/or prosthetic cardiac valve replacement in whom ECG changes and enzyme elevations are nondiagnostic

This study was undertaken to assess the usefulness of Tc PYP in man Its goals were to (1) ascertain the sensitivity of mTc PYP scintigraphy in patients with definite AMI as proved by the standard techniques (2) to assess the relative effectiveness of the technique for localizing the zone of infarction and (3) to evaluate the diagnostic usefulness in patients with other coronary artery disease syndromes but without AMI

Methods

Patient selection From August 1976 through September 1977 491 scintigrams were performed

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Table I Criteria for diagnosis of acute myocardial infarction

Includes all
1 Clinical history Sustained precordial chest pain unresponsive to nitrates occurring within 24 h of admission
2 Typical rise of serum CK GOT and LDH Maximum CK at least twice normal
3 *Transmural myocardial infarction* Development of Q waves of 0 04 sec duration with typical ST T wave changes
4 Nontransmural or subendocardial infarction Typical evolutionary ST T wave changes without new pathologic Q waves

Table II Criteria for interpretation of technetium 99m stannous pyrophosphate myocardial scintigrams

A Intensity grade		
	0	No accumulation of radionuclide in region of myocardium
	1+	Slight indefinite accumulation of radionuclide in the cardiac region
	2+	Definite accumulation of radionuclide in the region of the myocardium with activity less than that of ribs
	3+	Definite accumulation of radionuclide in the region of the myocardium with activity equal to that of the ribs
	4+	Definite accumulation of radionuclide in the region of the myocardium with activity greater than that of ribs
B Distribution		
	Diffuse—	Generalized radionuclide accumulation in the cardiac region apparently involving all aspects of the heart
	Discrete—	Radionuclide accumulation in a pecific region of myocardium

in 436 consecutive patients admitted to the Medical Intensive Care Unit of Rush-Presbyterian-St Luke s Medical Center for evaluation of chest pain and suspected acute myocardial infarction Patients with recent DC cardioversion or myocardial revascularization procedures were not included Cardiac specific isoenzymes were not obtained routinely therefore patients who received intramuscular injections or sustained muscle trauma were not included The patient population consisted of 310 men and 126 women—mean age (±SE) was 61 year ± 0 6 (range 33 to 90 years) All patients were evaluated by careful history and physical examination serial 12 lead electrocardiograms and serial serum enzyme determinations creatinine kinase (CK normal < 145 U /liter) serum glutamic oxalacetic transaminase (GOT normal < 35 units) and lactic dehydrogenase (LDH normal < 35 units) and lactic dehydrogenase (LDH normal < 220 units) Blood samples for serum enzymes were drawn and electrocardiograms were recorded at admission and daily for at least 3 consecutive days Electrocardiograms were also recorded after the first week and before discharge

Patients were divided into three groups Group I included patients with documented AMI Group II included patients without AMI and Group III included patients with uncertain diagnosis for AMI The criteria for the diagnosis of AMI are recorded in Table I Group II patients were further subdivided in four subgroups

1 Unstable angina defined as angina pectoris of new onset or changing in pattern and accompanied by transient ST T wave shifts during pain and no rise of serum CK GOT and LDH

2 Progressive angina defined as typical ischemic pain prompting hospitalization but without ST T wave shifts associated with pain

3 Stable angina occurring in patients with known atherosclerotic coronary artery disease who were hospitalized for intercurrent diseases or for elective cardiac catheterization

4 Noncardiac chest pain defined as chest pain which was not typically ischemic in character and was not associated with ECG changes or enzymes rise or when coronary arteriography showed normal coronary arteries Group III included patients in whom either the clinical presentation enzyme patterns or serial ECG changes were not clearly diagnostic of the presence or absence of infarction Several patients underwent left heart catheterization with left ventricular cineangiography and coronary arteriography in addition to the standard diagnostic studies

Instrumentation A Searle Radiographics mobile scintillation camera equipped with a medium resolution collimator (LEAP parallel hole) was used to perform imaging 90 to 120 minutes after the intravenous injection of 15 mCi of technetium 99m stannous pyrophosphate (Mallinckrodt Nuclear) With the exception of six patients who were scanned 12 to 24 hours after the onset of symptoms scintigrams were performed at the patient s bedside 24 to 120 hours after onset of symptoms The pulse height analyzer

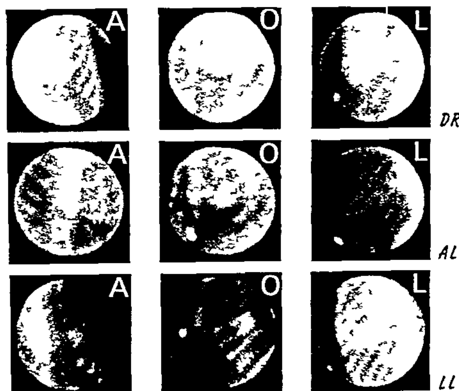


Fig 1 *Upper panel* Positive scintigrams showing the doughnut pattern in a patient with extensive anterior AMI Note the central defect surrounded by intense ^{99m}Tc PYP uptake in the anterolateral walls of the left ventricle A ^{99m}Tc PYP marker is evident in the xyphoid area the sternum ribs and vertebrae can be seen *Middle panel* Positive scintigrams in a patient with inferior AMI Note discrete uptake of ^{99m}Tc PYP in the inferior wall of the left ventricle *Lower panel* Positive scintigrams in a patient with posterior AMI Note discrete uptake in the posterolateral walls of the left ventricle *A* = Anterior view *O* = 45 degree left anterior oblique view *L* = left lateral view

centered on an energy corresponding to the 140 Kev photopeak of technetium 99m with a 20% window Imaging was performed in the anterior left anterior oblique (45 degree) and left lateral views accumulating 400 000 counts in each project The average duration of imaging in each patient was 20 minutes Follow up scintigrams were obtained in several patients up to 4 weeks after the initial study All scintigrams were clas sified according to the scheme devised by Parkey et al[1] (Table II) and were evaluated by three independent observers who had no previous knowledge of the patients clinical status Scinti grams with 2+ to 4+ uptake were considered positive regardless of distribution For purpose of data analysis a scintigram interpreted as positive by one observer and negative by the other two observers was considered negative Interobserver agreement in regard to positive and negative scintigrams was 90 In defining anatomical loca tion within the left ventricle of localized ^{99m}Tc PYP uptake bone landmarks such as sternum and vertebrae were used In order to compare radionuclide localization of infarction to the ECG localization a simplified ECG classification was used anterior (includes anterior anteroseptal and anterolateral ECG localizations) inferior (includes inferior and inferolateral ECG localiza tions) posterior (includes posterior and postero lateral ECG localizations) Fig 1 shows typical myocardial scintigrams in patients with anterior inferior and posterior AMI respectively

The data are presented as the mean ± 1 stan dard error of the mean Student s t test and chi square analysis were utilized to test for signif icant differences

Results

Group 1 Patients with acute myocardial infarction The scintigraphic results and enzyme determinations in 134 patients with AMI are shown in Table III Scintigrams were interpreted as positive in 78% of patients with a transmural AMI (83% of patients with anterior 73% of

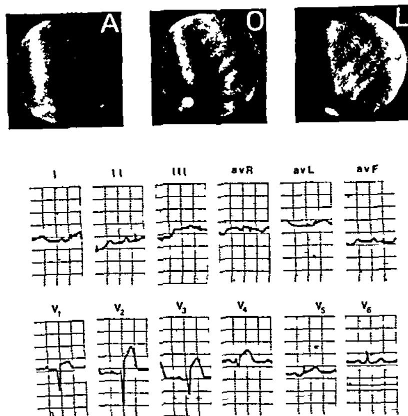


Fig 2 Scintigrams of a patient with anterior AMI recorded 3 days from onset of symptoms and approximately 48 hours from maximum CK (1?74 U) The electrocardiogram shows unequivocal evolving anteroseptal AMI Note excellent sternal and rib detail and no evidence of uptake in the region of the anterior wall

Table III Scintigraphic results and enzyme determinations in 134 patients with acute myocardial infarction

Patient group	Scintigram interpretation			Mean age (years ± SE)	Mean time of imaging (hours ± SE)	Max CK (U ± SE)	Max GOT (U ± SE)	Max LDH (U ± SE)
	Pos or neg	No pts	(%)					
Transmural AMI	Positive	76	(78)	59 ± 1	57 ± 4	1 86? ± 183	192 ± 15	823 ± 5?
	Negative	?1	(2?)	58 ± 2	5 ± 6	1 651 ± 272	287 ± 114	799 ± 204
Anterior	Positive	39	(83)	61 ± 3	57 ± 6	2,156 ± 298	255 ± 21	1 00? ± 94
	Negative	8	(17)	63 ± 5	58 ± 9	2,112 ± 600	595 ± 280	1 1?0 ± 511
Inferior	Positive	30	(73)	57 ± 6	53 ± 6	1 ?68 ± 190	138 ± 12	630 ± 52
	Negative	11	(27)	55 ± 3	53 ± 9	1,281 ± 211	86 ± 18	224 ± 68
Posterior	Positive	8	(80)	60 ± 4	66 ± 13	2 45? ± 608	256 ± 88	?06 ± 126
	Negative	2	(?0)	56	60	1 677	162	444
Non transmural AMI	Positive	15	(41)	60 ± 4	60 ± 8	1 47? 4?8	186 ± 34	651 ± 145
	Negative	2?	(59)	63 ± 3	57 ± 7	723 153	166 ± 51	533 ± 110

Abbreviations AMI = acute myocardial infarction CK = creatine kinase GOT = glutamic oxalacetic transaminase U = unit LDH = lactic dehydrogenase Max = maximum Pts = patients SE = standard error of mean

patients with inferior and 80% of patients with posterior AMI) and in 41% of those with a nontransmural AMI There were no statistical differences between patients with a positive and those with a negative scintigram with respect to mean age mean time of imaging from onset of symptoms and maximum CK GOT and LDH in each of the groups None of the patients with a false negative scintigram was studied later than 96 hours from the onset of symptoms

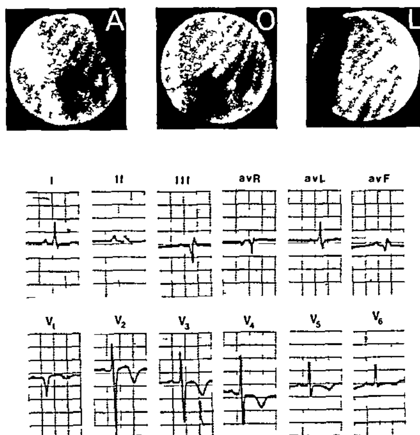


Fig 3 Scintigrams of a patient with unstable angina The electrocardiogram taken during an episode of chest pain shows ST T wave abnormalities in the precordial leads

Table IV Scintigraphic results in 226 patients without acute myocardial infarction

			Scintigram interpretation			
			Positive		*Negative*	
Patient group	*No of patients*	*Mean age (years ± SE)*	*No*	(%)	*No*	(%)
Unstable angina	32	59 ± 2.3	0	(0)	32	(100)
Progressive angina	86	63 ± 1.4	7	(8)	81	(9[illegible])
Stable angina	22	65 ± 2.2	2	(9)	20	(91)
Non cardiac pain	86	61 ± 1.5	2	(2)	84	(98)
Total	226	62 ± 1.0	11	(5)	215	(95)

The sensitivity of ^{99m}Tc PYP imaging in the detection of nontransmural AMI was significantly lower ($P < 0.01$) than in the detection of transmural AMI Maximum CK GOT and LDH previous history of angina pectoris and electrocardiographic evidence of a previous myocardial infarction were assessed in patients with transmural and in those with nontransmural AMI for differences that might account for the difference in sensitivity Patients with nontransmural AMI had significantly lower maximum CK ($P < 0.01$) than patients with transmural AMI Maximum GOT and LDH did not differ significantly between the two groups Patients with nontransmural AMI had a higher incidence of angina pectoris preceding the AMI than those with transmural AMI ($P < 0.01$) no difference was found between the two groups with respect to ECG evidence of a previous myocardial infarction

A diffuse ^{99m}Tc PYP uptake was found in only 10% (nine of 91) of patients with AMI and positive scintigrams six of these had a transmural AMI

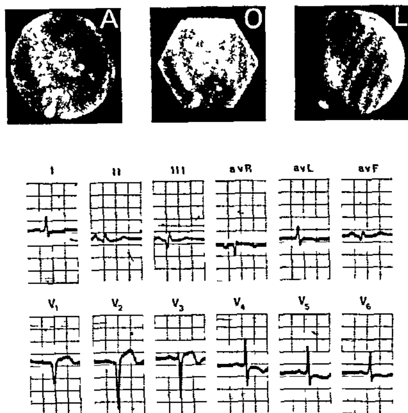


Fig 4 Positive scintigrams in the same patient as in *Fig 3* Note the electrocardiogram showing a pattern of AMI

and three had a nontransmural AMI In addition three patients with transmural AMI and two patients with nontransmural AMI had 1+ diffuse uptake Accurate ECG localization of AMI was possible only in patients with transmural infarction ^{99m}Tc PYP localized the site of infarction correctly in 70% (53 of 76) of patients with transmural infarction

Follow up scintigrams were obtained in 12 patients with AMI who had negative scintigram one to three days from the initial scintigram In three patients the second scintigram was interpreted as positive all three of them had a large transmural AMI and no ECG evidence of old myocardial infarction In nine patients the second scintigram remained negative five of them had a transmural AMI four of them a nontransmural AMI none of them had ECG evidence of old myocardial infarction In one patient with an anterior AMI and maximum CK of 1224 U scintigrams recorded at 24 48 72 hours from onset of symptoms were repeatedly negative (Fig 2)

Six patients with false negative ^{99m}Tc PYP scintigrams underwent left ventricular angiography and selective coronary arteriography 3 weeks to 3 months post infarction Three had an anterior AMI one an inferior AMI and two had a nontransmural AMI All patients had abnormalities of left ventricular contractility and significant coronary obstructive disease (> 75% luminal narrowing) of at least one major coronary artery One patient with cardiogenic shock had diffuse left ventricular hypokinesia and one patient had an apical aneurysm

Group II Patients without acute myocardial infarction The scintigraphic results in 226 patients without acute myocardial infarction are shown in Table IV Of 32 patients with unstable angina none had a positive scintigram of 86 patients with progressive angina 8% had a positive scintigram of 22 patients with pain 2% had a positive scintigram The specificity of ^{99m}Tc PYP imaging for the whole group was 95% ECG evidence of old myocardial infarction was present in 11 patients with unstable angina 49 patients with progressive angina (of which four had a false positive scintigram) and in 12 patients with

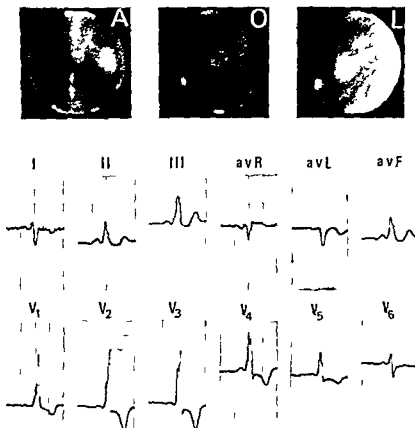


Fig 5 Scintigrams in a patient with WPW syndrome showing localized myocardial uptake in the anteroapical area Note the electrocardiogram showing type A WPW pattern

stable angina (of which two had a false positive scintigram) Of the 32 patients with unstable angina 9 patients subsequently developed an AMI Subsequently three died of the six who survived all had positive follow up scintigrams Fig 3 shows a negative scintigram and the electrocardiogram in a patient with unstable angina In the same patient scintigrams were positive several days later when he had developed an anterior AMI (Fig 4)

Of 11 patients without AMI who showed positive scintigrams six (54%) had a diffuse ^{99m}Tc PYP uptake and five had discrete uptake Six of 11 patients had ECG evidence of a previous myocardial infarction No patient with the clinical diagnosis of noncardiac chest pain showed discrete uptake

Group III Patients with uncertain diagnosis for AMI Seventy six patients had uncertain evidence for diagnosis of AMI In 11 patients intraventricular conduction disturbances precluded the ECG diagnosis of infarction (two patients had WPW syndrome and nine patients had left bundle branch block) The remaining 65 patients did not meet the criteria for infarction because they had cardiac enzymes elevation and no ECG changes or had ECG evidence of previous infarction or had ECG changes without typical rise of cardiac enzymes Scintigrams were interpreted as positive in 31 patients (48%) One of the two patients with WPW syndrome had a classical history and cardiac enzymes rise for myocardial infarction but no ECG changes In view of the strongly positive ^{99m}Tc PYP myocardial scintigram (Fig 5) localized in the anteroapical wall we felt it was appropriate to diagnose a myocardial infarction One patient with left bundle branch block had myocardial scintigraphy repeated at a 3 day interval following two episodes of pulmonary edema At the time of the second scintigram (Fig 6) which demonstrates uptake in the anterior wall the patient had had a rise of cardiac enzyme levels

Discussion

Our study shows the limited clinical value of ^{99m}Tc PYP myocardial scintigraphy in an unselected population admitted to a medical intensive

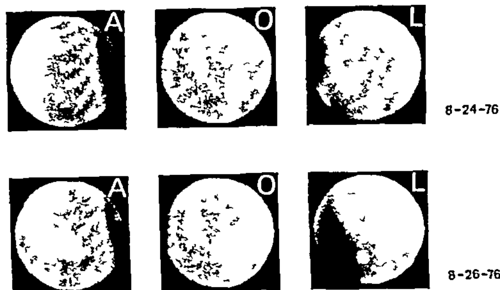


Fig 6 Scintigrams taken at 3 day interval in patient with LBBB and recurrent episodes of pulmonary edema Note localized myocardial uptake in the anterolateral wall on scintigrams *of the lower panel* At this time the patient had had a rise in cardiac enzymes

ire area for evaluation of chest pain and ispected myocardial infarction Although scin graphic localization of myocardial necrosis has een achieved with a number of technetium 99m omplexes including 99mTc tetracycline mTc lucoheptonate and gallium 67 citrate the major dvantages of 99mTc PYP is that imaging may be erformed within 60 to 90 minutes after injection f the radiopharmaceutical and that it has the ighest infarct to normal (25 1) concentration atios [1] Studies of humans with AMI report a ensitivity varying from 86% to 100% in patients vith transmural AMI and from 38% to .00% in patients with nontransmural AMI

Despite careful attention to the purity of the radiopharmaceutical agent which was assessed by the chromatographic method and the technical quality of our imaging procedure we found that myocardial scintigraphy correctly identified acute infarction in only 78% of patients with transmural AMI and only 41% of patients with nontransmural AMI Timing between the onset of infarction and obtaining a mTc PYP scinti gram is of considerable importance and it was optimal in our study (the average time being between 2 and 3 days post onset of symptoms) Previous investigators have suggested that 12 hours is the earliest time after onset of symptoms for accurate detection of infarction Although in our study no patient with a negative scintigram was scanned before 24 hours from onset of symp toms three out of 12 follow up studies of patients with initial negative scintigrams converted to positive It appears that in certain patients the initial positive scintigram may not be seen until four five or more days after the onset of symp toms Perhaps in such patients some collateral flow develops later in time allowing for enhanced delivery of 99mTc PYP

In addition there was no apparent relationship between severity of infarction and negative scinti grams within each patient subgroup as assessed by determination of cardiac enzymes However patients with nontransmural AMI had signifi cantly lower maximum CK than patients with transmural AMI supporting the hypothesis that the former group of patients sustained relatively small infarcts The significance of false negative scintigrams is unknown We believe that the sensitivity of mTc PYP imaging does not depend solely on infarct size but upon other factors as well such as the extent of myocardial fibrosis and coronary obstructive disease the development of collateral flow into the area of irreversible damage and the possibility that mechanisms other than calcium binding may all contribute to concentration of mTc PYP in irreversibly dam aged myocardial cells

In support of the above hypothesis are postmortem findings of a patient who died

myocardial wall rupture after a massive anterior infarct and who had a negative scintigram (in preparation) The patient had severe triple vessel disease and histologic examination revealed acute infarct of the lower half of the septal and anterior wall In addition there were multiple tiny areas of acute infarct in the remaining ventricular wall and old infarct of the upper portion of the anteroseptal wall and interstitial fibrosis of the lateral and posterior walls of the left ventricle Postmortem tracer studies demonstrated tracer concentration ratios higher than 7 1 between acutely infarcted myocardium and normal myocardium only in the left ventricular apex (total weight 9 0 g 1 5% of the heart weight)

Classification criteria for a positive scintigram may also significantly vary the sensitivity and specificity of the test The interpretation of 2+ diffuse pattern has been difficult and is considered equivocal rather than definitively positive or definitively negative[3] Willerson and associates[3] showed that this pattern is common in patients with nontransmural AMI and Donsky and colleagues[1] reported it in 35% of patients with unstable angina It is probable that investigators will differ slightly in their interpretation of these diffusely positive scans However the small number of diffusely positive scintigrams and the fact that we interpreted as positive 2+ diffuse uptake exclude the possibility that the lower sensitivity in detecting AMI in our study might be secondary to more strict criteria for scintigram interpretation

A diffuse pattern (2+ diffuse uptake) has been reported to persist in 41 to 47% of patients with a positive myocardial scintigram during AMI[3, 35] Such persistent positive ^{99m}Tc PYP scintigrams frequently correlate with progressive myocardial damage and might be an important prognostic indicator of a complicated postinfarct clinical course In addition a diffuse pattern has been reported to occur in up to 13% of patients without the clinical syndromes of coronary artery disease and may be due to blood pool imaging[3] In patients with heart disease a diffuse pattern has been reported in patients with valvular calcification[3] stable angina cardiomyopathy and after DC cardioversion However the occurrence of a discrete pattern in patients without AMI occurs almost exclusively in patients with heart disease associated with previous myocardial necrosis including ventricular aneurysm Our data in part support those studies since all five patients with false positive scintigrams and discrete uptake had a history of previous myocardial infarction

The need of a sensitive and specific test for myocardial necrosis is underscored by the number of patients in which the diagnosis of AMI could not be confirmed with certainty using standard ECG and enzyme criteria This points to the difficulty of differentiating among the variety of coronary artery disease syndromes In patients with ventricular conduction abnormalities such as WPW syndrome LBBB or paced rhythm the electrocardiogram is often not helpful In those patients who have a typical history of prolonged chest pain associated with ST wave depression and/or T wave inversion lasting more than 24 hours it is difficult to assume a diagnosis of myocardial infarction in the absence of cardiac enzymes elevations Likewise elevation of cardiac enzymes may not always be of diagnostic accuracy in patients who have just undergone coronary artery revascularization Our experience with ^{99m}Tc PYP imaging in patients with ventricular conduction abnormalities is encouraging Others have reported encouraging results in patients with perioperative myocardial infarction[5]

In summing up in our series the following conclusions seem warranted

1 ^{99m}Tc PYP imaging is moderately sensitive in detecting and localizing transmural AMI and is insensitive in detecting nontransmural AMI

2 a discrete ^{99m}Tc PYP uptake is highly specific for AMI

3 A diffuse uptake is neither sensitive to nor specific for AMI

Myocardial imaging with ^{99m}Tc PYP appears most helpful in those clinical circumstances in which routine diagnostic techniques are inadequate for a confident diagnosis of myocardial infarction

Summary

Technetium 99m stannous pyrophosphate (^{99m}Tc PYP) myocardial imaging was performed in 436 consecutive patients for the evaluation of chest pain and suspected acute myocardial infarction (AMI) Scintigrams were assessed independently by three observers with a 90% interobserver agreement In 134 patients with documented AMI (97 transmural 37 nontransmural) the sensitivity of ^{99m}Tc PYP imaging was significant

ly lower in patients with nontransmural AMI (41%) than in patients with transmural AMI (78%) ^{99m}Tc PYP imaging correctly localized the site of transmural infarction in 53 patients (70%) A diffuse ^{99m}Tc PYP uptake was found in nine (10%) of 91 patients with positive scintigrams six of these had a transmural AMI and three nontransmural AMI In 226 patients without AMI the specificity of infarct imaging was 95% A false positive scintigram was found in 0% 8% 9% and 2% of patients with unstable angina progressive angina stable angina and noncardiac chest pain respectively A diffuse uptake was found in six (54%) of 11 patients with false positive scintigrams No patient with the clinical diagnosis of noncardiac chest pain showed discrete uptake In 76 patients with uncertain diagnosis for AMI ^{99m}Tc PYP imaging was considered of value in 11 patients with ventricular conduction defects (two patients with WPW syndrome nine patients with LBBB) These data suggest that

1 ^{99m}Tc PYP imaging is moderately sensitive in detecting and localizing transmural AMI and is insensitive in detecting nontransmural AMI

2 A discrete ^{99m}Tc PYP uptake is highly specific for AMI

3 a diffuse uptake is neither sensitive to nor specific for AMI

Myocardial imaging with ^{99m}Tc PYP is of clinical value when the standard electrocardiographic and enzymatic techniques are inadequate for an accurate diagnosis of AMI

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The comparison between non-invasive and invasive methods of stroke volume determination in children

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The stroke volume (SV) is a parameter widely used to assess over all myocardial function The ability to accurately estimate SV in a non invasive manner would be helpful in dynamic clinical situations such as the postoperative state The purpose of this study was to evaluate how SV obtained by echocardiography and radio nuclide angiography compared with SV obtained at cardiac catheterization We used the Fick principle dye dilution methods and contrast angiography as the invasive techniques for comparison

Patients and methods

Twenty three children aged 3½ to 20 years (mean 10 3 ± 4 9 years) formed the study group These children had coarctation of the aorta either pre or postoperatively and were being studied because of hypertension Parental consent was obtained for all children under 16 years of age Those over 16 signed consent for themselves Echocardiograms and nuclear angiograms were performed on all 23 patients Cardiac catheteriza tion was then performed on 21 of the patients within the next 24 hours

Echocardiograms were obtained using either an Ekoline 20 or Hoffrel 101C ultrasonoscope inter faced with a Cambridge recorder Patients were studied supine and in the shallow right anterior oblique position Left ventricular dimensions to the nearest millimeter were taken at the point just inferior to the mitral valve echo Measure ments from three cycles were averaged These measurements were done by two observers and the data were compared Any deviation of greater than 1 mm was re checked Echocardiographic volumes were derived by two methods The end diastolic and end systolic dimensions were cubed (E) The second method utilized the regression equation derived for children by Meyer and asso ciates (E) The echocardiographic stroke volume was the difference between end diastolic volume and end systolic volume as calculated by each method

Radionuclide angiograms were obtained on the same day as were the echocardiograms Techne tium 99 m labelled albumin was injected as a bolus into the right external jugular vein or right antecubital vein A least squares fit to a gamma variate function of the time activity curve gener ated from the first pass through the left ventricle was analyzed after dead space correction was done The cardiac output was calculated The stroke volume (R) was obtained by dividing the cardiac output by the heart rate

Cardiac catheterization was carried out under sedation A cocktail of meperidine 15 mg /ml cholorpromazine 6 25 mg /ml and promethazine 6 25 mg /ml in a dose of 0 1 ml /Kg body weight to a maximum of 2 ml was used [2] Dye dilution

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Table I Stroke volume (ml) for each method of assessment

Patient No	*D*	*F*	*A*	*E*	*E*	*R*
1	30 3	22 3	34 2	29 0	38 5	28 0
2	35 6	35 4	32 8	44 2	52 8	52 0
3	22 8	19 5	16 5	36 0	47 7	
4	51 2	41 5	25 0	38 7	55 3	
5	23 9	22 8	23 0	22 1	28 2	
6	83 1	63 1	88 4	71 4	75 9	
7	57 6	44 1	39 9	38 5	44 3	50 5
8	46 6	31 1	26 9	48 6	54 9	43 0
9	64 7	45 0	36 9	50 2	54 5	65 0
10		68 2	70 3	90 9	87 0	
11		70 5	60 8	46 4	49 2	52 6
12	64 2	81 6	65 3	59 8	60 4	52 0
13	58 2	41 9	96 0	49 2	54 5	
14		59 7	75 0	54 4	55 6	44 0
15	82 1	46 0	85 4	68 8	73 2	
16	25 6	28 5	25 3	22 2	30 4	
17	80 0	104 7	87 9	90 6	83 9	84 4
18	55 4	69 2	64 4	57 5	57 5	87 0
19				60 3	55 6	87 0
20	90 0	83 9	71 9	36 9	41 8	91 0
21		34 7	41 0	41 1	45 9	31 8
22				27 9	36 3	52 0
23	13 1	12 5	31 7	22 2	30 6	41 0

Abbreviations D = dye dilut on F = Fick A = contrast angiography E = echo cubic dimensions E = echo regression equation R = radionuclide angiogr phy

curves were obtained following the injection of indocyanine green into the main pulmonary artery Blood was withdrawn from the left ventricle and passed through a Waters cuvette model DCU 303 The area under the curve was calculated according to the formula of Williams and colleagues The heart rate was calculated from a simultaneous electrocardiogram and the stroke volume (D) equalled the cardiac output divided by the heart rate

Oxygen consumption was measured on a Kipp and Zonen Diapharometer BA4 During this time blood for oxygen saturation was withdrawn simultaneously from the main pulmonary artery and aorta and was analyzed on a Co oximeter IL 182 Instrumentation Laboratory Inc Cardiac output was then calculated by the Fick principle Stroke volume was determined by dividing this cardiac output by the heart rate obtained during the time of oxygen consumption (F)

After these procedures biplane left ventricular cineangiograms in the anteroposterior and lateral views were filmed on either Siemens or Phillips equipment These were the initial angiograms taken A calibration grid was also filmed for each injection to standardize the magnification factor for each patient The left ventricular end-diastolic and end systolic volumes were calculated by tracing frames from the cineangiograms with a sonic pen digitizer interfaced with a Nova 2/10 computer The program used was derived from the work of Sandler and co workers[5] The angiographic stroke volume (A) equalled the end diastolic volume minus the end systolic volume

Results

The stroke volumes derived by each method are shown in Table I Dye curves were usable in 17 of the 21 patients catheterized In three patients minimal aortic regurgitation was present In one patient equipment failure prevented assessment The radionuclide angiograms were technically satisfactory in 15 patients Fick and angiographic stroke volumes were calculated in all 21 patients catheterized A matrix of correlation coefficients was constructed to compare each of the methods of stroke volume determination to each other (Table II) The p values were obtained by Student s t test[6] for each r value (Table II) All values were statistically significant at less than the 0 05 level except E_1 vs R

Discussion

The parameters of myocardial performance are usually derived invasively None of the methods of measurement of SV can be defined as an absolute reference standard We cannot therefore estimate the accuracy of any non invasive technique in the determination of SV Each method of SV estimation requires assumptions that at best result in an approximation of SV Because of differences in the derivation and application of each technique one would expect a less than perfect regression correlation where comparing one to the other[7]

The calculation of cardiac output by the Fick principle requires measurements that take several minutes to perform The arteriovenous oxygen difference at any one time may not represent the steady state that is assumed The use of indocyanine green dye also has many potential errors in calculation that limit its accuracy Factors such as varying cardiac output during the withdrawal period rate of withdrawal appearance time mixing of the dye with blood and variatio s

of the volume of injected dye may all compromise the final result [9]

The accuracy of radionuclide angiography is limited by fragmentation of the bolus and background radiation The technique must be considered relatively invasive due to the intrinsic radiation hazards and the preferred site of injection the external jugular vein In this study the bolus was carefully monitored and only those patients in whom it was judged adequately compact were assessed In vivo labelling of red blood cells with Tc 99m after pretreatment with pyrophosphate has been shown to give a more efficient label with decreased risk of dissociation [10, 11] The estimation of background activity is difficult but its accurate quantification is essential to the correct estimate of stroke volume Dead time correction was instituted because of losses of up to 25 per cent of the tracer during the first transit

Angiographic contrast materials affect ventricular function [13, 14] Extrasystoles commonly occur immediately during the injection of contrast into the left ventricle Once the post extrasystolic beat has occurred the alteration of cardiac function has already taken place [1] Even when the levo phase of right sided injections are used optimal ventricular visualization usually takes several cycles to occur

Assumptions are made in the M mode echocardiographic determination that also limit its accuracy [7] The minor axis determination in infants and children requires a different regression equation to compensate for the altered ventricular geometry Our results tend to favor the straight cube method when compared to the other estimations This probably reflects the older age of many of our patients Inadvertent recording of papillary muscles and oblique transducer angulation also hamper accuracy [1] The use of a real time two dimensional ultrasonic scanner enables one to visualize the long axis as well as the minor axis of the ventricle and may avoid these problems [9] Echocardiography however does have the advantage of enabling one to calculate the stroke volume on individual beats without the use of cardiotoxic agents

The formulae used for determination of ventricular volumes have all used either other invasive techniques or autopsy specimens for their derivations and suffer from the same inaccuracies as their reference standards

Table II Correlation matrix r values and corresponding p values

	F	*A*	*E*	*E*	*R*
D	.82 p < 001	.80 p < 001	76 p < 001	76 p < 001	78 p < 01
F		73 p < 001	72 p < 001	66 p < 01	75 p < 01
A			72 p < 001	68 p < 001	64 p < 02
E				.98 p < 001	.54 p < 05
E					47 p < 1

Abbreviations as in T ble I

Previous work comparing invasive or non invasive estimates of cardiac output has been done primarily in adults The estimates relied on similar pulse rates during the two determinations In our patients the pulse rates during cardiac catheterization were generally lower than during the echocardiograms Pulse rates during nuclear angiography were the highest and were probably related to the unsettling effect of an injection into the right external jugular vein

When we compared the outputs as calculated by the various methods there was no significant correlation obtained Only when each value was normalized for heart rate i e stroke volume was the significant correlation obtained This is because stroke volume tends to remain constant despite variation of heart rate that may occur with changes in position temperature and degree of sedation

Despite all of the potential sites for inaccuracy echocardiography and nuclear angiography provide SV estimates which correlate as well as the invasive techniques do to each other Echocardiography provides the clinician with a method which is practical for repetitive evaluations in a particular patient There is neither risk nor trauma to the patient Therapeutic interventions can be objectively evaluated Portable nuclear imaging equipment may provide similar ease of utilization in the near future

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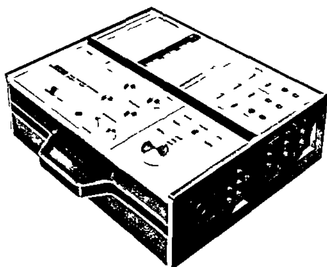
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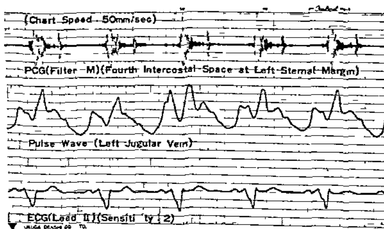
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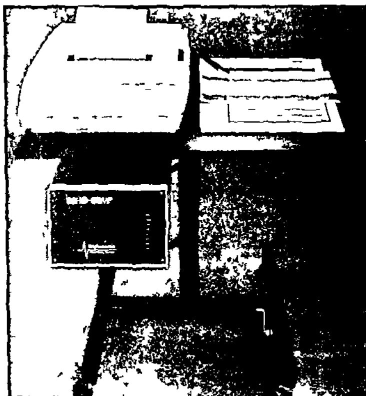
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Case reports

Treatment of a case of lanatoside C intoxication with digoxin-specific $F(ab')_2$ antibody fragments

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Digitalis poisoning is common symptoms of intoxication occur in 10 to 20 per cent of all patients treated with cardiac glycosides The lethality ranges from 5 per cent to 10 per cent [1] Until now treatment has been limited to symptomatic measures [1]

In in vitro and in animal experiments the pharmacological and toxic effects of cardiac glycosides can be reversed by means of specific antibodies [1] [1] Digoxin specific antibodies had previously been employed clinically on only one occasion namely in a patient who had taken an overdose of digoxin with suicidal intent and who had failed to respond to conventional symptomatic treatment [4] The present paper describes the use of F(ab) fragments of digoxin specific antibodies to treat a patient with severe coronary heart disease who developed lanatoside C intoxication as a result of overdosage

Case report

On May 1 1978 an 87 year old woman suffering from coronary heart disease was admitted to hospital after going into heart failure associated with nausea vomiting and visual disturbances For several years she had been taking 24 drops (= 0 8 mg) of lanatoside C daily A few days before hospitalization her heart failure had worsened after a period of prolonged chest pain and the dosage of lanatoside C was raised to 24 drops, three times daily a total dose of 2 4 mg per day

On admission the patient who weighed 4?.9 kilograms and was 151 cm tall was mentally alert but in a debilitated state Her blood pressure was 1?0/?0 mm Hg and her pulse was irregular at 110/minute The left ventricle was enlarged and signs of heart failure were present basilar rales over the lungs liver enlarged and tender bilateral pleural effusions and ventricular gallop

Blood sedimentation rate hematocrit sodium potassium blood gases and creatine phosphokinase were normal Urinary nitrogen transaminases betahydroxybutyric dehydrogenase and alkaline phosphatase were slightly increased The creatinine clearance was 4o ml /min /1 73M at a plasma creatinine level of 1 07 mg /100 ml The WBC was slightly raised but without a shift to the left Apart from 5 to 20 red blood cells in the sediment the results of urinalysis were within the normal range

On admission the ECG revealed chaotic atrial tachycardia at a rate of about 110/minute (Fig 1A) pronounced rounded ST depression signs of left ventricular hypertrophy and a subacute infarction of the lateral wall. At this time the serum digoxin concentration was 8 9 ng /ml

In the 24 hours following admission to hospital, the state of the patient did not improve despite administration of potassion diuretics, and oxygen No antiarrhythmic drugs were given Disorders of conduction (second and third degree atrioventricular blocks) and ventricular extrasystoles, sometimes occurring in runs now developed (Fig 1B C D) On May 2 1978 the digoxin level was still 5 9 ng /ml. The possibility of inserting a temporary endovenous pacemaker was considered however with the consent of the patient who had not previously been treated with heterologous serum it was decided to institute treatment with digoxin specific antibodies

Methods

Production of antibodies Digoxin was coupled to human serum albumin as described previously Yearling sheep were

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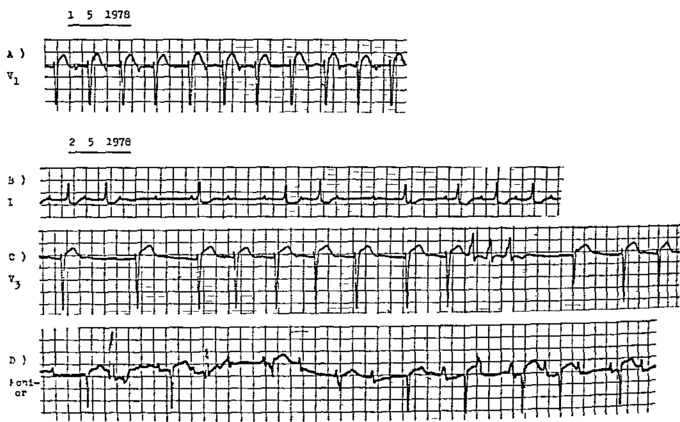


Fig 1 Rhythm disturbances in the electrocardiogram (25 mm /sec) before commencement of treatment with digoxin specific antibodies *A* Chaotic atrial tachycardia *B* Second and third degree atrioventricular block *C* Run of ventricular extrasystoles *D* Third-degree atrioventricular block ventricular extrasystoles and escape beats second degree type I atrioventricular block

immunized with 3 mg of the digoxin–albumin conjugate in Freund s complete adjuvant and boosted with the same doses at intervals of 14 days Blood was sampled every 2 weeks

Digoxin pecific gammaglobulin was precipitated from antidigoxin antiserum with ammonium sulphate at 35 per cent saturation F(ab) fragments were prepared by enzymat ic cleavage of the gammaglobulin fraction with pepsin The digoxin pecific F(ab) fragments were isolated by means of an immunoadsorbent consisting of an ouabain–ribonu clease-Sepharose 4 B conjugate The F(ab) fragments were then separated from intact IgG by fractionation on Sephadex G 200

The F(ab) preparation was found to be sterile pyrogen free and non toxic (as tested in accordance with the European Pharmacopoeia) and the limulus test (in accordance with FDA regulations) was negative It was stored at −70 C

Immediately before administration 500 mg of the F(ab) antibody fragments were made up to 500 ml of infusion solution with 5 per cent dextrose

Measurement of the serum digoxin concentration Blood was sampled from a central venous catheter on the day before and immediately before the start of the antibody treatment During the F(ab) infusion blood wa sampled h urly from a peripheral vein After the infu ion samples wer taken at less frequent int rvals The serum di oxin co n entrati ons were determined b radioimmunoassay on the ame d y

Evaluation f the antibodies t sheep F(ab) The antibod ies to sheep F(ab) and sheep IgG were evaluated by passive hemagglutination F(ab) and IgG were coupled to sheep red blood cells using bisdiazotised benzidine The patient s serum was inactivated by incubation at 56 C for 30 minutes. Positive tests were carried out using rabbit antiserum to sheep IgG

Results The patient s general condition pulse rate blood pressure central venous pressure respiration temperature and electrocardiogram were monitored continuously during the intravenous drip infusion of the F(ab) fragments of digoxin specific antibodies which were given drop-wise at first then at an increasing rate of up to 32 drops per minute (= 96 ml /hour) over a total period of 5½ hours The total dose was 460 mg F(ab) in 460 ml 5 per cent dextrose (Fig 2) No untoward effects were reported by the patient, nor were any side effects observed The heart failure did not deteriorate during or after the infusion of the antibodies. Eighty minutes after the start of the antibody infusion when a dose of 64 mg F(ab) had been administered sinus rhythm associated with first degree atrioventricular block (PQ interval 0 24 sec) was reinstated for the first time for a period of 10 minu es and was then interrupted by second and third-degree atrioventricular block As the infusion continued conduction showed constant improvement and after 280 minutes sinus rhythm was perma nently established with a PQ interval of 0.23 sec which decreased a few hours later to 0 20 sec (Fig 3) The patient remained in sinus rhythm The subsequent clinical course was

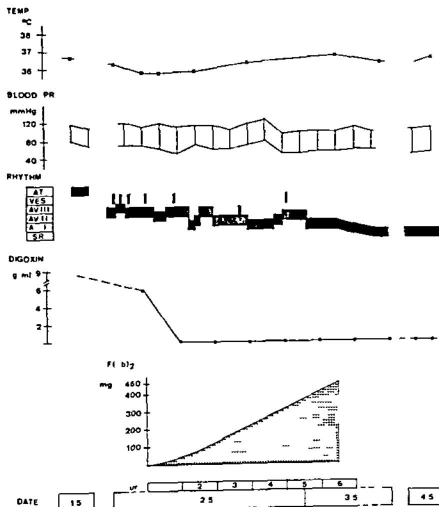


Fig 2 Temperature *(TEMP)* blood pressure *(BLOOD PR)* cardiac rhythm *(RHYTHM)* and plasma digoxin concentration *(DIGOXIN)* during infusion of F(ab) fragments of digoxin specific antibodies. *AT* = chaotic atrial tachycardia *VES* = ventricular extrasystoles *AV I AV II AV III* = first second and third-degree atrioventricular block *SR* = sinus rhythm

uneventful and in particular no signs of intolerance to the animal antibody preparations were observed Immediately before the start of the antibody treatment the plasma digoxin concentration measured by radioimmunoassay was 5 9 ng /ml One hour after the start of the F(ab) infusion and on the following days no free digoxin was detectable (Fig 2)

Four weeks after the treatment the patient s serum agglutinated erythrocytes coated with sheep F(ab) with a titer of 1 8

Discussion

Glycoside specific antibodies may be used to reverse the pharmacological and toxic effects of cardiac glycosides [11] Intact antibodies are not needed for this purpose F(ab) or Fab fragments are equally effective both in vitro and in animal experiments [1] [1] but have the advantage that they are more rapidly distributed over the body compartments have a shorter half life and owing to the absence of the Fc component have reduced immunogenicity Moreover complexes of digoxin and specific Fab fragments would appear to be excreted more rapidly with the urine than the intact antibody complexes thus ensuring more rapid elimination of the digoxin from the organism The effect of F(ab) fragments on glycoside kinetics has still to be investigated

Potentially lethal arrhythmias induced by digoxin in animals were terminated with digoxin specific antibodies within one hour In man immunotherapy using Fab antibody fragments has been employed on only one previous occasion namely in a case of attempted suicide with a massive overdose of digoxin [11]

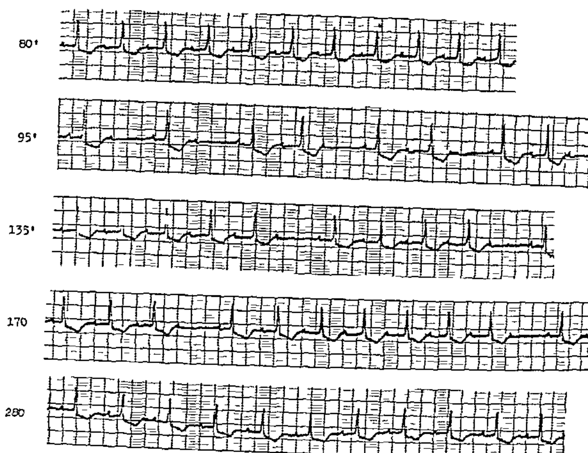


Fig 3 Flectrocardiogram (Lead I 25 mm/sec) during infusion of F(ab) fragments of digoxin specific antibodies (*80' 95* etc = minutes after start of the infusion)

The case described in this paper was one of accidental *intoxication* with lanatoside C Only a small fraction *of this* naturally occurring glyco side from *Digitalis lanata* is absorbed unchanged into the blood *stream after oral* administration the greater part being *converted by the* intestinal flora mainly *into digoxin* and acetyldigoxin and absorbed as such All three compounds share an identical steroid *nucleus* and thus react with digoxin specific antibodies

In our *patient digitalis* intoxication was confirmed by the *case history* the symptoms the rhythm disturbance *and the digoxin blood* levels which were well up in the *toxic range* In view of the grave and uncertain *prognosis it was decided* to institute treatment [illegible]ith F(ab) *fragments of* digoxin specific antibodies instead of the usual symptomatic *measures* Eighty minutes after the start of the *antibody infusion* sinus rhythm with a first degree atrioventricular block was restored for a short time [illegible] second and third degree atrioventricular block *again* supervened As the infusion continu[illegible] *arrhythmia and* sinus rhythm alternated the normal rhythm becoming increasingly predominant until finally after 280 minutes sinus rhythm was permanently reinstated This course of events largely conforms to observations in animal experiments in which there is commonly some delay before normal rhythm is re established [11] The only difference is the longer time elapsing before onset of the therapeutic effect which may be ascribed to the slower administration of the antibody In keeping with the findings in animal experiments[1] and in the patient treated with Fab fragments [11] free digoxin was no longer detectable one hour after the start of infusion Since an excess of antibody was administered it might have been expected to nullify not only the toxic but also the therapeutic effect of the glycoside However the heart failure did not worsen during or after treatment No side effects attributable to the heterologous antibody preparation occurred during or after the infusion However four weeks after treatment a very low titer of antibodies to sheep F(ab), fragments was detectable in the patient s blood

The use of fragments of antibodies to cardiac glycosides permits specific treatment of digitalis intoxication When symptomatic treatment is given the associated arrhythmia may persist for two to three days in digoxin intoxication and for a still longer period in digitoxin intoxication However administration of the antibody fragments terminates digitalis induced arrhythmia within a few hours The advantages of immunotherapy must be weighed against the possible occurrence of side effects and the risks involved in treatment with heterologous antibodies Severe anaphylactic shock and delayed reactions of the serum sickness type are rare with purified horse and bovine sera containing only antibody fragments [1] No reliable data are as yet available for ovine sera

Summary

In animal experiments arrhythmias induced by cardiac glycosides which prove fatal if untreated can be terminated by administration of glycoside specific antibodies Immunotherapy with digoxin specific antibody fragments had hitherto only been employed on one occasion namely in a person who had taken a massive overdose of digoxin with suicidal intent and who had failed to respond to symptomatic treatment

The present paper describes the use of F(ab) fragments of digoxin specific antibodies in a female patient with lanatoside C intoxication to treat the associated life threatening cardiac arrhythmia The arrhythmia was rapidly terminated and normal sinus rhythm was restored Treatment with the heterologous antibodies did not cause any side effects

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The post-pulmonary infarction syndrome

Herschel J Sklaroff M D
New York N Y

William Dressler described the occurrence of pericarditis several days weeks or months following myocardial infarction—a syndrome that now bears his name The etiology is unknown although immune mechanisms have been suggested This type of pericarditis is often accompanied by fever a rapid erythrocyte sedimentation rate pleural effusions and friction rubs and rarely by pulmonary infiltrates hemoptysis arthralgias arthritis myalgias and/or unexplained anemia The administration of corticosteroids results in prompt resolution of the signs and symptoms of the Dressler syndrome and is so dramatic as to be virtually diagnostic of its presence

Three patients have been observed who manifested a Dressler like syndrome associated with a persistent pleural effusion following pulmonary infarction which responded dramatically to corticosteroid therapy This appears to be a distinct clinical entity and may be appropriately named the Post Pulmonary Infarction syndrome

Case reports

Case No 1 L B was 68 years old in January 1966 when she developed the sudden onset of hemoptysis and severe left pleuritic chest pain Serial electrocardiograms revealed only sinus tachycardia and nonspecific S-T and T wave changes An x ray film of the chest revealed bilateral pleural effusions and a Fleishner line in the left lower lung field A left thoracocentesis recovered serosanguineous fluid and heparin therapy was instituted for presumed pulmonary thromboembolism with infarction On the third hospital day the temperature rose to 102 F and penicillin was administered for possible infection complicating pulmonary infarction however during the following three weeks a clinical picture evolved that included daily fever between 101 and 102 F severe pericardial pain associated with n intermittent pericardial friction rub severe bilateral pleuritic pain and pleural friction rubs a persistent left pleural effusion and a sedimentation rate of 108 mm /hr (Westergren)

The possibility of a Dressler syndrome complicating a pulmonary infarction was entertained and corticosteroid therapy was begun Eight milligrams of dexamethasone were administered intramuscularly and in six hours the patient was completely relieved of her pains Corticosteroid therapy was continued for two weeks, during which time the patient remained afebrile and pain free The pleural effusion disappeared and the erythrocyte sedimentation rate returned to normal. The corticosteroids were then abruptly discontinued and in five days the syndrome recurred in its entirety including the left plerual effusion Reinstitution of corticosteroid therapy once again achieved a prompt and dramatic clinical result

Case No 2 M S had Saint Vitus dance as a child While in her fifties she developed the signs and symptoms of congestive heart failure and was found to have auricular fibrillation with mitral stenosis and mitral regurgitation Her symptoms were easily controlled with digitalis and diuretics In February 1966 she experienced the sudden onset of hemopty is and right pleuritic chest pain (Fig *1a*) and was treated with heparin for presumed pulmonary thromboembolism with infarction Several weeks later acute left pleuritic chest pain occurred (Fig *1b*) associated with hemoptysis and dyspnea A left pleural effusion was present clinically and radiographically and serial electrocardiograms revealed transient right axis deviation Heparin therapy was reinstituted The pleuritic pain and pleural effusion persi ted and several days later fever and the classical pain of pericarditis associated with a loud pericardial friction rub developed

The possibility of a Dressler syndrome complicating pulmonary infarction was considered and 8 mg of dexamethasone were given intramuscularly In six hours the patient wa pain free The dexamethasone was continued orally for two weeks (Fig *1c*) during which time the patient was afebrile and asymptomatic and the pleural effusion resolved. Six days following the abrupt discontinuation of the corticosteroids (Fig *1d*) the syndrome recurred in its entirety including the pleural effusion With reinstitution of the corticosteroids (Fig *1e*) the syndrome again vanished dramatically The corticosteroids were continued for several week and then the dose was gradually tapered without recurrence of the syndrome

Case No 3 B E is a f3 year-old woman who was well until January 197f when she experienced acute left pleuritic chest pain An electrocardiogram and x ray film of the chest were normal The pain persisted and a second x ray film of the chest taken two weeks lat r (Fig *2a*) revealed a Fleishner line

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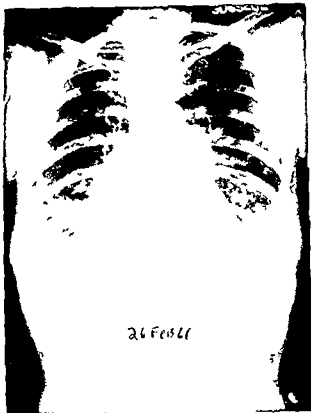


Fig 1a Case No 2 X ray film of chest made on Feb 26 1966 There is a wedge shaped infiltrate in the right lower lung field associated with hemoptysis and right pleuritic chest pain



Fig 1b Case No 2 X ray film of chest made on March 8 1966 There is left pleural effusion associated with hemoptysis and left pleuritic chest pain

in the left lower lung field The pain increased in severity and one month later a third x ray film of the chest was unremarkable During the following month the patient had daily fever between 100 6 and 10? F and sustained a 15 pound weight loss

On March 3 1976 the temperature was 101 F paroxysmal auricular fibrillation occurred a loud pericardial friction rub was heard signs of a left pleural effusion were present the white blood cell count was 24 000 with 80% polys and the erythrocyte sedimentation rate was 89 mm /hr (Westergren) A roentgenogram of the chest revealed bilateral Fleishner lines (Fig 2*b*) and a left pleural effusion A lung scan (Fig 3*a*) revealed a defect in the left lower and left upper lung fields The pleural fluid was an exudate and was sterile Pleural biopsies were negative for tumor and tuberculosis A cell block made from the pleural fluid was negative and pleural cultures were also negative Intravenous Keflin was given for ten days with no result A repeat lung scan (Fig 3*b*) showed clearing of the left upper lobe defect After one month s hospitalization the clinical picture was unchanged—the fever pleural effusion and pleuritic chest pain remained (Fig 2*c*)

The possibility of a Dressler like syndrome following pulmonary infarction was considered and 30 mg of prednisone were given daily The pain and fever subsided in 24 hours and the pleural effusion vanished in one week (Fig 2*d*) Two months later the patient was afebrile and pain free had gained ten pounds and had a normal x ray film of the chest



Fig 1c Case No 2 X ray film of chest made on March 19 1966 The x ray was made several days following corticosteroid therapy for persistent pleural effusion fever and signs and symptoms of pericarditis



Fig 1d Case No 2 X ray film of chest made on March 28 1966 There is recurrent left pleural effusion five days after corticosteroid withdrawal associated with pain of pericarditis



Fig 1e C[illegible] No [illegible] X[illegible] film of chest made on April 13 19[illegible] There [illegible] appar[illegible] [illegible] effusion following reinstitution of corti[illegible]roid

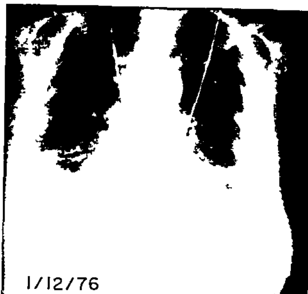


Fig 2a Case No 3 X ray film of chest made on January 12 1976 There is a Fleishner line apparent in the left lower lung field associated with left pleuritic chest pain



Fig 2b Case No 3 X ray film of chest made on March 9 1976 Bilateral Fleishner lines are apparent with left pleural effusion left pleuritic chest pain and pericardial friction rub

(Fig 2e) white blood cell count and erythrocyte sedimentation rate The prednisone was gradually discontinued with no recurrence of the syndrome

Discussion

These three patients exhibited many of the usual clinical features of pulmonary thromboembolism with infarction The unusual features of their illness were the persistent fever and pleural

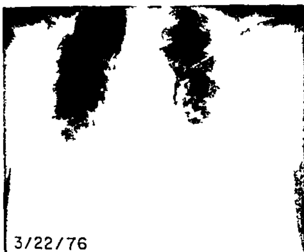


Fig 2c Case No 3 X ray film of chest made on March 2? 19 6 There is persistent large left pleural effusion

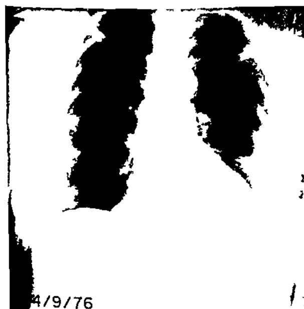


Fig 2d Case No 3 X ray film of chest made on April 9 19/6 The chest appears normal one week following institution of corticosteroid therapy



Fig 2e Case No 3 X ray film of chest made on June 11 19/6 The chest appears normal one month following discontinuation of corticosteroids



Fig 3a Case No 3 Initial perfusion lung scan shows defects in the right lower left lower and left upper lobes

effusion the occurrence of pericarditis and the dramatic response of their illness to corticosteroid therapy Of interest is that each pleural effusion was in the left chest (Fig 4) perhaps explaining the advent of an associated pericarditis solely on an anatomical basis

Whatever the pathogenesis of the Dressler syndrome following myocardial infarction it is likely that a similar mechanism is operative in the persistent fever pleural effusion and pericarditis seen in these patients following pulmonary infarction The importance of early recognition of the Post Pulmonary Infarction syndrome lies in its dramatic response to corticosteroid therapy (which like the Dressler syndrome is virtually diagnostic of its presence) thereby affording almost instant relief to the patient and appreciably shortening the duration of the illness

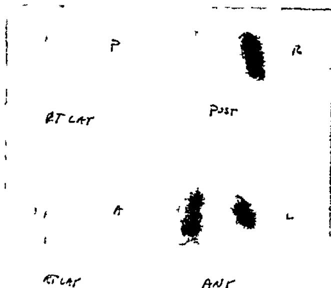


Fig 3b Case No 3 Second perfusion lung scan shows clearing of the right lower and left upper lobe defects

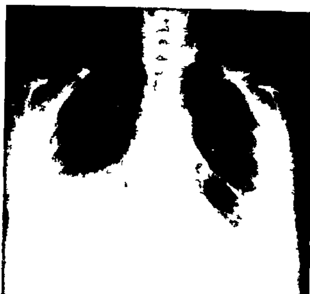


Fig 4 Case No 3 X ray film of chest demonstrating close proximity of pericardium to pleura in the left chest

Summary

Following pulmonary infarction three patients developed the classical signs and symptoms of the Dressler syndrome associated with persistent left pleural effusion Each responded dramatically to corticosteroid therapy While the pathogenesis of this Post Pulmonary Infarction syndrome like the Dressler syndrome is unclear the response to corticosteroid therapy is both dramatic and diagnostic and may spare the patient prolonged discomfort and unnecessary diagnostic procedures

Addendum

Anticoagulant therapy should probably be continued in these patients as in patients with uncomplicated pulmonary thromboembolism for the risk of recurrent embolization far outweighs the risk of creating a significant hemothorax

Clinical pathologic conference

Diabetes mellitus malabsorption and congestive heart failure in a middle-aged man A case of thesaurosclerosis

Jerome Koss M D
Stephen M Factor M D
Bronx N Y

Case presentation

This 62 year old man was first admitted to the Bronx Municipal Hospital Center in June 1974 with a several week history of weight loss diarrhea and weakness He had a four year history of diabetes mellitus requiring insulin (44 units NPH/day) and had frequent hypoglycemic episodes For the three years prior to admission the patient had congestive heart failure manifested by peripheral edema pleural effusion and dyspnea on exertion requiring digitalis and diuretic therapy The past medical history was negative for hypertension chest pain or palpitations There was no history of alcoholism

The patient was in his usual state of health until four weeks prior to admission when he developed diarrhea characterized by frequent loose foul smelling stools He lost 12 pounds despite an excellent appetite

On admission the patient was noted to be a cachectic white male in no acute distress The blood pressure was 110/70 the pulse 64/minute and irregular the respiratory rate 16/minute and the temperature 37° C The skin was slightly yellow There was no jugular venous distension The chest was clear The point of maximum cardiac impulse was felt in the sixth intercostal space in the mid clavicular line Several observers described a Grade II III/VI holosystolic apical murmur radiating to the left The liver was palpated 2 cm below the right costal margin A prominent epigastric mass was felt below the xiphoid process The spleen was not palpable Bowel sounds were hyperactive The testes were small

Initial laboratory data showed hemoglobin 13 9 gm per cent and hematocrit 41 6 per cent WBC was 6 600 with 69 neutrophils 28 lymphocytes 2 monocytes and 1 eosinophil Urinalysis had 3+ glucose Serum sodium was 135 mEq /L potassium 3 7 mEq /L chloride 98 mEq /L CO content 27 mM /L BUN 9 mg per cent creatinine 0 6 mg per cent and glucose 250 mg per cent The calcium was 8 9 mg per cent phosphate 2 6 mg per cent uric acid 1 9 mg per cent total bilirubin 0 8 mg per cent prothrombin time 13 7 seconds and the partial thromboplastin time 45 seconds The alkaline phosphatase was 138 units LDH 210 units SGOT 123 units SGPT 75 units and CPK 40 units Serum carotene was zero Amylase was 60 units The total protein was 7 5 gm per cent with albumin 4 0 gm per cent The serum iron was 210 with the total iron binding capacity 270 Thyroid function tests were within normal limits

The electrocardiogram revealed flutter-fibrillation at a rate of 60/minute There were occasional premature ventricular contractions There was poor R wave progression across the precordium The chest roentgenogram on admission showed cardiomegaly

During his initial hospitalization the patient underwent a liver-spleen scan which showed hepatosplenomegaly with an area of decreased activity in the area of the porta hepatis A barium

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enema showed no intrinsic lesions but there was extrinsic pressure on the transverse colon An upper gastrointestinal series showed a mid epigastric mass displacing the duodenal sweep with a normal small bowel Superior mesenteric artery and celiac arteriogram showed calcification in the head of the pancreas an enlarged liver with a prominent left lobe an enlarged spleen a suggestion of tortuous coronary varices in the gastric fundus and no evidence of tumor in the liver or pancreas A D xylose absorption test was normal Secretin test showed a markedly increased volume and decreased bicarbonate production Small bowel biopsy showed no pathology Before discharge another diagnostic procedure was performed

Clinical discussion

DR JEROME KOSS In preparing this Clinical Pathologic Conference I have felt not unlike William Osler did about syphilis that to know this case is to know internal medicine This case spans such a wide variety of disease processes and organ systems that I will have to play Sherlock Holmes though without his wit or cleverness in attempting to analyze the relevant clues to reach a diagnosis

The first possible clue is that the patient had a four year history of diabetes mellitus with frequent episodes of hypoglycemia Though genetic diabetes mellitus is by far the most common etiology of glucose tolerance it is the responsibility of the internist to consider other potential causes Included in this list are Cushing s syndrome acromegaly pheochromocytoma as well as hemochromatosis and cirrhosis all of which are associated with insulin resistance whereas patients with chronic pancreatitis a rather common etiology of diabetes mellitus in our alcoholic population have insulin sensitivity This sensitivity is felt to be secondary to alpha cell destruction and hence low levels of glucose[1] Since this patient was known to have frequent hypoglycemic episodes pancreatic insufficiency should be considered as a possible cause

In addition to diabetes mellitus this patient had congestive heart failure manifested by dyspnea on exertion peripheral edema and pleural effusions He was normotensive but had an enlarged heart and a holosystolic murmur consistent with mitral regurgitation The electrocardiogram revealed atrial fibrillation occasional ventricular premature contractions and poor R wave progression Of note is the lack of chest pain hypertension, palpitations or history of rheumatic fever or alcoholism

The most common cause of congestive heart failure in a patient of this age is ischemic heart disease with previous myocardial infarction In favor of this diagnosis is the presence of diabetes mellitus the atrial fibrillation which is a frequent arrhythmia in these patients and the poor R wave progression which is suggestive of an old myocardial infarction The murmur of mitral insufficiency is consistent with papillary muscle dysfunction secondary to ischemia The absence of chest pain is perhaps explained by the old clinical maxim that diabetics have an increased incidence of silent myocardial infarctions In addition the entity of ischemic cardiomyopathy has been proposed to describe patients with severe congestive heart failure without chest pain who have documented coronary artery disease on angiography or postmortem examination[2]

Despite these considerations I feel that there are several points against the diagnosis of ischemic heart disease Recent studies indicate that diabetics really do not have any greater incidence of silent infarctions than the rest of the population[3] In addition there is no definitive evidence of a previous myocardial infarction on the electrocardiogram poor R wave progression may be mistaken for previous infarction but it is often explained by other mechanisms

Valvular heart disease specifically mitral regurgitation secondary to rheumatic heart disease must be considered The absence of a history of rheumatic fever should not deter us from considering this diagnosis Frequently such patients can present for the first time with congestive heart failure in the 40 to 60 age range[4] Atrial fibrillation is certainly a common arrhythmia in these patients Against this diagnosis however are the absence of mitral stenosis or other valvular lesions the lack of calcification on chest x ray and the fact that the left atrial size was not remarkable Furthermore since the murmur was not well characterized it is possible that it was the result of altered ventricular hemodynamics rather than a fixed structural abnormality

I believe that this patient most probably had primary myocardial disease specifically congestive cardiomyopathy Patients with congestive

cardiomyopathy often have signs and symptoms of both right and left sided congestive failure with dilated and flabby hearts They frequently develop functional mitral regurgitation second ary to dilatation of the ventricle and valve ring Atrial fibrillation with ventricular premature contractions are the most common rhythms observed Finally poor R wave progression or so called pseudoinfarction pattern is also fre quently associated with this condition All of these were present in the patient discussed today

Although the differential diagnosis of conges tive cardiomyopathy includes an extensive list of diseases this patient s extracardiac symptomatol ogy make several conditions attractive possibili ties particularly since they are popular diagnoses at CPC s

Primary amyloidosis usually presents as a restrictive cardiomyopathy which may simulate constrictive pericarditis However when amyloid disease is extensive left ventricular systolic func tion may be compromised leading to low cardiac output and cardiomegaly along with typical low voltage on ECG and congestive heart failure refractory to medical management Sarcoidosis may also cause congestive cardiomyopathy but typically patients with sarcoid heart disease are characterized by the development of severe atrioventricular conduction disease which may lead to sudden death Hemochromatosis is anoth er cause of congestive cardiomyopathy which we will discuss subsequently

With the background of diabetes mellitus and congestive heart failure we are now confronted with the immediate problems that brought this patient to the hospital He presented with features of intestinal malabsorption as well as yellow skin small testes elevated hepatic enzymes but normal bilirubin abnormal iron and iron binding capacity and an enlarged liver The extensive radiologic evaluation revealed the presence of hepatosplenomegaly varices consis tent with portal hypertension and no evidence of tumor in the pancreas or liver The hepatic disease and portal hypertension are unlikely to be the result of either congestive heart failure or neoplastic disease Sarcoidosis involving the liver is probably ruled out by the absence of lymphad enopathy pulmonary disease skin findings and the nature of the cardiac disease Amyloidosis can explain the congestive heart failure the hepato splenomegaly and the malabsorption but portal hypertension is not a usual manifestation of this disease Hemochromatosis mentioned previously in the discussion of diabetes mellitus and conges tive heart failure is a known cause of hepatomeg aly and cirrhosis that will require further consid eration

Several observations of this patient on his admission to the hospital require comment The yellow skin brings only a few entities to mind Jaundice the most common cause was not pres ent in our patient Carotenemia secondary to hypothyroidism or to certain diets rich in carrots can be eliminated by the zero carotene level obtained in the work up of malabsorption Atabrine used in the therapy of malaria may cause a yellow discoloration of the skin but is not relevant to this case Finally patients with hemochromatosis rarely may be described as having yellow skin it must be stressed however that the usual skin discoloration is bronze or dark brown secondary to melanin or slate gray second ary to iron deposition in the dermis The increased serum iron and transferrin saturation raise our suspicions about hemochromatosis However it should be remembered that iron overload is found in patients with alcoholic cir rhosis In addition in one study of healthy subjects elevated serum iron greater than 200 μg percent was noted Some of these subjects were found to have abnormal liver function tests of unknown significance [5]

Malabsorption is the final aspect of the case and one which I believe to be the most intriguing and unusual The history is classic weight loss despite a good appetite and the passage of frequent yellow foul smelling stools consistent with steatorrhea The differential diagnosis of malabsorption is extensive and spans the alpha bet from amyloid to Zollinger Ellison syndrome Despite this extensive list the work up is one of the more rewarding in medicine since it is simple organized and in this case gives me a specific answer

Calcium albumin and prothrombin time are general screening tests which may raise the suspi cion for malabsorption if they are abnormal but they do not localize the problem They also may be normal as in our patient despite significant malabsorption

Twenty four hour fecal fat which was not performed is the most accurate measurement of

steatorrhea and may give a clue as to the site of the absorptive defect Very abnormal fecal fat excretion (more than 25 gm) suggests pancreatic disease while smaller amounts (12 to 15 gm) suggest biliary tract or jejunal disease The D xylose test an imperfect measure of carbohydrate absorption is felt to be an indicator of jejunal mucosal function Patients with pancreatic disease with rare exception have a normal D xylose test[6] The presence of a normal test in our patient shifts our focus away from the small intestine and toward the bile salts and pancreas The negative upper GI series and small bowel biopsy lend further support to this notion

The secretin test a measure of pancreatic function further localizes the problem to the pancreas Our patient had an abnormal test characterized by a low bicarbonate concentration and a high water output This has been reported to occur in patients with idiopathic hemochromatosis but without clinical malabsorption[7] An additional finding the observation of calcifications in the pancreas noted on the upper GI and angiographic study confirms the pancreas as the site of malabsorption

The causes of pancreatic exocrine insufficiency include pancreatic carcinoma pancreatectomy, cystic fibrosis and chronic pancreatitis Pancreatic carcinoma is unlikely with the normal angiogram while cystic fibrosis although it can occur in adults usually is associated with prominent pulmonary symptoms The most common etiology of chronic pancreatitis is alcoholism which may lead to recurrent attacks of acute pancreatitis and abdominal pain Besides the negative history of alcohol intake in this patient there was no history of abdominal pain This lack of pain also serves to rule out several other causes of pancreatitis such as hyperlipidemia hypercalcemia hereditary pancreatitis and idiopathic pancreatitis which generally present with abdominal pain as a major feature of the disease Although painless pancreatitis does occur I am compelled to discount this and to consider idiopathic hemochromatosis as the etiology because of the other findings in this case

Idiopathic hemochromatosis is a disease of iron overload of unknown etiology It is felt to be inherited as an autosomal dominant Many close relatives exhibit elevated serum iron levels without overt evidence of disease The pathogenesis of iron overload is poorly understood Most authorities feel that iron overload is related to a metabolic defect in which iron absorption from the gut is increased and in which iron deposition in tissues causes pathological damage

What are the clinical features of idiopathic hemochromatosis and how do they explain the findings in the patient we are discussing?

Diabetes mellitus was the first major clinical disease in this case It occurs in 30 per cent of patients as the initial manifestation of idiopathic hemochromatosis and eventually develops in 75 per cent of cases[10, 11] On occasion it may occur in patients with hemochromatosis who also have a genetic deposition to this disease Generally however it is felt to result from impaired glucose tolerance and insulin sensitivity secondary to associated cirrhosis as well as pancreatic iron overload and damage to beta cells[10, 11]

The diabetes of hemochromatosis is difficult to control and has a high incidence of insulin resistance perhaps related to cirrhosis The case being discussed had insulin sensitivity with bouts of hypoglycemia I believe this was related to significant pancreatic damage which may have affected levels of glucagon as well as insulin In addition insulin sensitivity may be related to relative endocrine deficiency Pituitary insufficiency may occur in 20 per cent of patients with hemochromatosis and it may explain the small testes observed in this group as well as in the case discussed today[12] Patients with pituitary insufficiency, unlike cirrhotics have decreased FSH LH and cortisol levels[12]

An important feature of idiopathic hemochromatosis is the development of congestive heart failure The older literature questioned whether iron deposits in the heart were of functional significance citing cases of heavy iron deposition with little fibrosis and no congestive heart failure[13] However Buja and Roberts[14] reviewed 19 patients with hemochromatosis and concluded that cardiac iron deposits were always associated with dysfunction with the degree of dysfunction dependent on the quantity of iron present in individual fibers as well as the number of fibers involved Fifty per cent of patients with idiopathic hemochromatosis will eventually develop congestive heart failure and in 15 per cent of cases it is the presenting feature of the disease Rarely patients may present with a restrictive cardiomyopathy simulating constrictive pericarditis[1] but most often they present with the

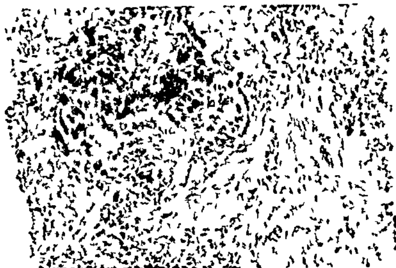


Fig 1 An area of the liver biopsy which initially confirmed the diagnosis of hemochromatosis reveals a regenerative nodule of liver cells completely surrounded by dense collagen Iron pigment is present in virtually every hepatocyte darkening the cytoplasm in this black and white photograph (Masson s trichrome stain original magnification ×125)

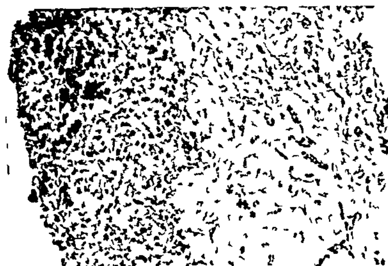


Fig 2 This section of the liver biopsy stained for iron pigment reveals a striking discrepancy between the heavily iron laden hepatocytes and the relatively iron free stroma A few proliferating bile ducts in the fibrotic area also contain dark staining iron granules This pattern of iron deposition is considered by some to be a feature of idiopathic hemochromatosis (Perl s iron stain original magnification ×125)

features of congestive cardiomyopathy They develop a dilated thickened myocardium leading to biventricular failure The electrocardiogram in addition to poor R wave progression may show low voltage There is a high incidence of supraventricular arrhythmias correlated with the extent of iron deposition in the atrial wall the conduction fibers and particularly the sinoatrial node are relatively spared from iron deposition compared to the working myocardium

Recently Henry and associates[16] detected cardiac abnormalities on echocardiography in patients with hemochromatosis before any other clinical signs of myocardial disease were evident These patients had increases in left ventricular wall thickness and transverse diameter and left atrial size months before the development of overt congestive heart failure Today congestive heart failure has overtaken diabetes mellitus and hepatic disease as the most common cause of

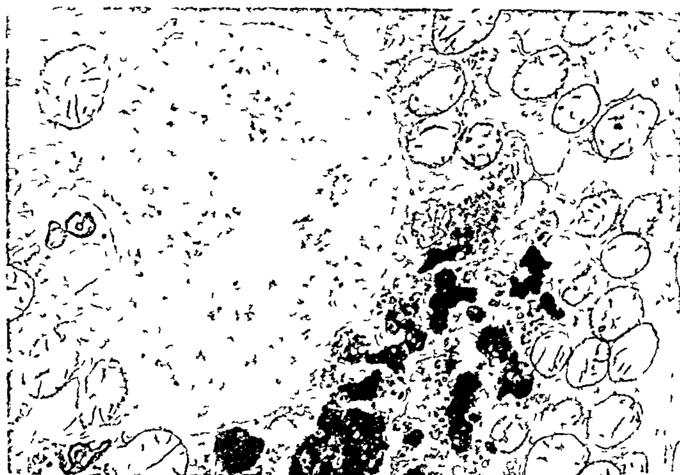


Fig 3 This electron micrograph of the postmortem liver specimen reveals numerous aggregates of electron-dense iron granules in the perinuclear zone of this hepatocyte Although it cannot be appreciated at this magnification most of the pi ment as well as other debris is present within membrane bounded structures con i tent with lysosomes The mitochondria demonstrate moderate di ruption of cristae and some loss of matrix In general, despite the four hour period between death and tissue fixation the tissue is well preserved (Original magnification ×14 000)

morbidity and mortality in patients with idiopathic hemochromatosis Phlebotomy has been reported to be useful in treating the congestive heart failure as well as other manifestations of the disease but many patients still succumb to cardiac failure

Hepatomegaly and cirrhosis occur in most patients with idiopathic hemochromatosis but hepatic function remains surprisingly good Primary hepatic carcinoma occurs in 15 per cent of patients as a late complication and cannot be entirely ruled out in this case The most intriguing aspect of today s case is the chronic pancreatitis and malabsorption Although as I mentioned patients with idiopathic hemochromatosis often have evidence f exocrine insufficiency without overt malabsorp n this patient probably represents the s l case described with malabsorption secondary to hemochromatosis[1]

In summary I believe that this patient had idiopathic hemochromatosis Prior to discharge he probably had a liver biopsy which I predict revealed cirrhosis with significant iron deposition in the reticulo-endothelial and parenchymal cells His course after discharge was probably a gradual downhill one resulting in uncontrollable congestive heart failure and death

Pathology findings

DR STEPHEN M FACTOR As Dr Koss surmised the diagnostic procedure performed during the first hospital admission was a liver biopsy which established the diagnosis The biopsy revealed increased portal fibrosis which was more severe in some areas than in others Even without an iron stain it is apparent that there is

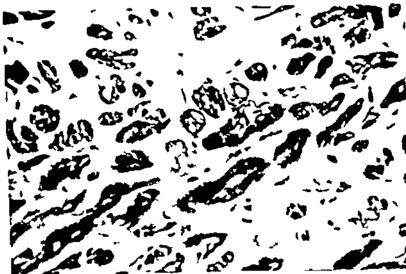


Fig. 4. This section of myocardium reveals extensive interstitial fibrosis with wide separation of the myofibers. The myocardial cells are generally hypertrophied and vacuolated, although atrophied and degenerated cells are also present. (Masson's trichrome stain, original magnification ×125.)

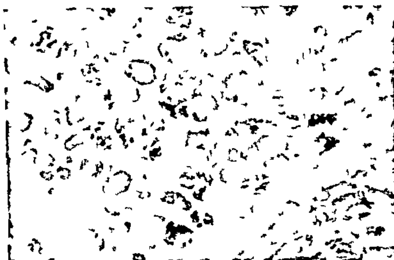


Fig. 5. This iron stained section of subepicardial myocardium demonstrates the heavy deposition of dark iron pigment within the myocardial fibers. In general, there was more pronounced iron deposition in the subepicardial muscle than in other areas of the heart. (Perl's iron stain, original magnification ×125.)

increased pigment within the parenchymal cells and bile ducts (Fig. 1). There are many situations in which iron is present in the liver either as a primary condition or secondary to endogenous or exogenous overload. The specificity of the iron and its localization in relation to the diagnosis of idiopathic hemochromatosis versus hemosiderosis has been debated for years. Although it is not an absolute criterion for diagnosis in familial or primary hemochromatosis, iron is found predominantly in parenchymal cells of the liver, pancreas, heart, and endocrine organs, and less so in the reticulo-endothelial system.[9] Thus, in the liver less iron is concentrated in the stroma. This can be seen in this case in which the iron stain reveals a discrepancy between parenchymal versus stromal iron deposition (Fig. 2).

The patient was followed for 18 months with periodic clinic visits until he presented with shortness of breath, fever, and chills. During a several

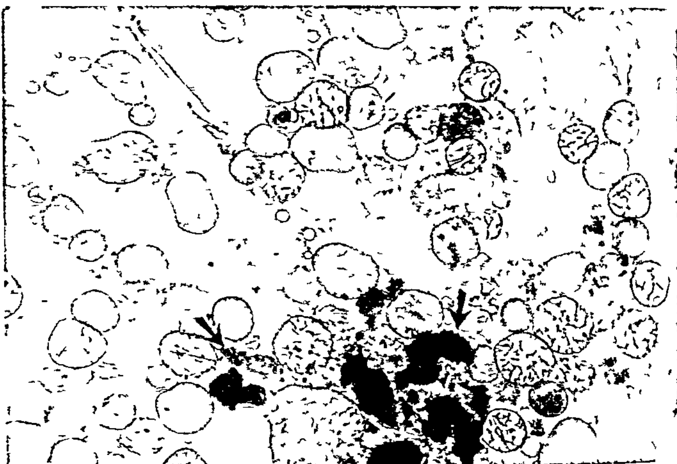


Fig 6 Th electron micrograph of a relatively well preserved myocardial cell demonstrates two characteristic features of iron-storage disease The iron is present within membrane-bounded bodies (arrows) consistent with lysosomes and many mitochondria are swollen, with disruption of cristae and loss of mitochondrial matrix density Although the latter finding may represent autolytic change the proximity of normal and degenerated mitochondria suggests that the alterations may be secondary to antemortem events (Original magnification ×14 000)

week hospital course he had marked lability of his blood sugar questionable hypoadrenalism supraventricular arrhythmias and middle lobe pneumonia He died of pneumonia while the diagnostic work up was proceeding

At postmortem the liver weighed 1,200 grams and had a typical rusty brown appearance with a micronodular pattern of cirrhosis. The histological appearance was identical to the biopsy specimen and revealed marked deposition of iron within the parenchyma We examined the liver by electron microscopy and demonstrated the presence of electron-dense ferritin granules and hemosiderin generally within membrane bounded vacuoles consistent with lysosomes (Fig 3) Despite the fact that this was postmortem tissue the preservation was remarkable even after four hours. The changes in the parenchymal cells consisted mainly of mitochondrial alterations similar to mitochondrial degeneration described in the hearts of four patients with hemochromatosis We cannot entirely rule out the possibility that the mitochondrial swelling was a result of postmortem autolysis. How intralysosomal iron leads to mitochondrial damage and extracellular fibrosis is unknown However the fact that hemochromatosis is a lysosomal storage disease may provide some clues to the pathogenesis of collagen deposition Other lysosomal storage diseases are also associated with fibrogenesis a point that I will return to shortly

The patient had obvious pigmentation of the extremities. The skin showed iron deposited in a perivascular location as well as within sweat ducts It is generally accepted however that the increased pigmentation (bronzing) manifested

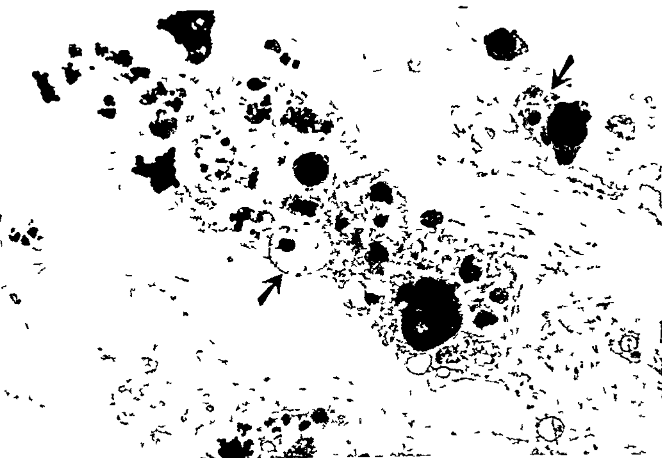


Fig 7 This area of the liver reveals a group of interstitial cells heavily laden with electron-dense iron granules surrounded by compact collagen fibers Many of the iron granules clearly are present within membrane bounded tructures consistent with lysosomes (arrows) (Original magnification ×14 000)

by these patients is a result of dermal melanin deposition possibly related to abnormalities of the pituitary-adrenal axis He had heavy deposits of iron in the adrenal cortex which may have contributed to his clinically apparent hypoadrenalism We were not granted permission to examine the cranial contents and therefore we could not evaluate the pituitary gland

In regard to the etiology of malabsorption the pancreas was markedly atrophied and dark brown in color Large pigmented peripancreatic lymph nodes also were noted a characteristic feature of this disease The pancreas was severely involved with extensive fibrosis and only rare scattered remnants of ductular acinar and islet tissue were present The gastrointestinal tract was uninvolved with the exception of the gastric mucosa which had iron pigment—again a typical feature of hemochromatosis in contrast to hemosiderosis Thus we feel confident that malabsorption was a result of exocrine pancreatic insufficiency—a rare complication of this disease as Dr Ross pointed out

The heart weighed 335 grams and was not overtly hypertrophied Although cardiac hypertrophy has been described in this disease the iron laden heart is often normal or only slightly increased in weight The epicardial adipose tissue was absent consonant with this patient s severe cachexia (body weight 100 lbs) The coronary arteries were widely patent and tortuous An incidental finding which played no role in the development of cardiac failure was the presence of a single coronary ostium giving rise to both coronary arteries

The heart was dilated and flabby consistent with a congestive cardiomyopathy and it was rusty brown in color secondary to iron deposition The mitral valve had non specific thickening a feature of several of the lysosomal storage

diseases which we have been studying The valvular alterations did not appear severe enough to account for mitral insufficiency rather the valve incompetence was probably on a functional basis Histologically there was extensive interstitial fibrosis with hypertrophy and vacuolization of myofibers (Fig 4) Iron pigment varied from area to area with heavier deposition in the subepicardium than in the midwall consistent with Buja and Roberts observations[14] (Fig 5)

Although iron was present within the vacuolated and presumably injured fibers it was difficult to correlate the degree of tissue damage with the extent of iron deposition Despite this caveat there now can be no question that iron is toxic to the myocardium and leads to a true cardiomyopathy Whether myocardial failure results from damage to the metabolic apparatus of the myocardial cell or follows from the extensive collagen deposition in the interstitium will require further study Despite the ease in which electron-dense iron particles can be visualized by the electron microscope few studies of myocardial ultrastructure in hemochromatosis have been performed. Perhaps the only systematic study was published by several French workers who described mitochondrial degeneration in the myocardial cells We studied the ultrastructure of formalin fixed myocardium from this patient and we also demonstrated mitochondrial abnormalities consisting of focal edema and loss of cristae associated with cellular vacuolization (Fig 6) in cells with intra lysosomal iron storage In the absence of fresh biopsy tissue or an animal model of myocardial hemochromatosis the artefactual nature of these changes must be considered strongly

Another possible mechanism of myocardial functional damage relates to the prominent interstitial fibrosis observed in hemochromatosis and noted in this case (Fig 7) How lysosomal storage of iron leads to fibrosis in the heart liver pancreas and other organs is an intriguing question which has interested several of us here at Einstein Doctors Goldfischer Biempica and I have been studying a group of diseases typified by lysosomal storage of non degraded substrate including iron associated with prominent vascular and/or parenchymal connective tissue proliferation We have coined the term thesaurosclerosis based on two Greek roots meaning storage and hardness to characterize these diseases Several well known hereditary storage disorders including Morquio s syndrome and Hurler s disease are in this category as well as acquired conditions such as asbestosis silicosis and possibly even atherosclerosis It appears that hemochromatosis a hereditary disease in which non degraded iron is stored in lysosomes in association with parenchymal fibrosis also should be included in this group of diseases

How lysosomal storage of iron leads to parenchymal fibrosis is speculative It is possible that stored materials may lead to leakage of lysosomal proteolytic enzymes and increased cell damage or death stimulating a reparative response of the tissue One group has reported that several lysosomal hydrolytic enzymes are increased in hemochromatosis and that the lysosomes containing iron are leakier than normal[10] It is also possible that stored materials may affect levels of lysosomal enzymes specifically required for collagen synthesis and degradation Collagenase binding to collagen for instance has recently been implicated in the reversibility or irreversibility of experimentally induced cirrhosis[3]

It is clear that the study of diseases such as hemochromatosis typified by the case presented today can provide us with invaluable clues regarding the pathogenesis of tissue injury in general. If we could comprehend the mechanism of fibrogenesis in hemochromatosis we might gain important insights into the development of connective tissue deposition in other storage disorders including atherosclerosis

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Fundamentals of clinical cardiology

Cardiopulmonary resuscitation an algorithm and some common pitfalls

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Cardiopulmonary resuscitation (CPR) techniques are intended to revive individuals who have experienced an unexpected respiratory or circulatory catastrophe They should not be used to prolong terminal and irreversible disease states

In the past two decades revolutionary advances in basic understanding techniques, teaching and practice of CPR have resulted in saving countless lives However broad involvement of physicians from all specialties paramedical personnel and the general public brought parascientific agencies and politics into the decision making process regarding scientific guidelines[1,2] Clear concepts and simple techniques have become unnecessarily confused and complicated Even the proceedings of the Wolf Creek Conference during which 24 of the initiators of modern CPR met in October 1975 reflect the confusion and conflicting recommendations which result from generalizations based upon impressions gained from differing conditions of clinical practice laboratory preparations testimonial evidence and inappropriate inference

There is not even general agreement on the definition of the frequently used term cardiac arrest Confusion and conflicting recommendations could be reduced if the term were limited to "the sudden and unexpected cessation of myocardial contractility for a period of at least sixty (60) seconds It would then be clear that the Stokes Adams attack which persists long enough for development of myocardial hypoxia profound hypotension which may be clinically indistinguishable from cardiac arrest, and asystole with or without persistent electrocardiographic activity all require the same approach to resuscitation The basic principles of CPR are clear and straightforward but application must be adapted to specific circumstances

Among the many causes of sudden death are drowning electrocution smoke and gas inhalation drug or chemical intoxication anaphylaxis cerebrovascular accidents injuries of the head neck or chest coronary occlusion convulsions and unconsciousness from any cause Asphyxia generalized or localized in a particular tissue such as the myocardium is either the cause or the inevitable consequence of any form of sudden death Resuscitation is usually a problem in oxygen transport from air to tissue with myocardial reoxygenation holding highest priority since without restoration of myocardial contractility all other considerations are in vain

During experimental obstructive asphyxia[3] four distinct stages may be observed Immediately after obstruction of the airway breathing efforts continue Only relief of the obstruction is needed to effect resuscitation After two to four minutes of obstruction breathing efforts stop while circulation continues intact At this stage relief of obstruction and ventilation of the lungs with air result in resuscitation If obstruction continues for six to nine minutes severe hypotension and bradycardia lead to pulselessness dilated pupils and absent heart sounds Artificial ventilation if quickly given often is life saving However this stage is transient and myocardial contractions cease even though reasonably normal electrocardiographic activity usually continues for prolonged periods Once myocardial contractions stop artificial ventilation and circu

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lation usually with drug therapy are needed for resuscitation This sequence and the resuscitative measures which are effective at each stage simulate many clinical events

Obviously when circulatory arrest is not preceded by an asphyxial episode and immediate corrective measures can be applied successfully preliminary reoxygenation is unnecessary and wastes time for example *when a monitored* patient develops ventricular fibrillation and external countershock can be applied without delay However if successful correction is not accomplished within one to two minutes myocardial hypoxia makes artificial ventilation and circulation possibly with drug therapy necessary preliminaries to successful defibrillation Clinical death occurs when the victim s heart stops beating but cellular metabolism continues for a limited period of time thereafter Irreversible changes occur in the vital tissues unless effective artificial ventilation and circulation are promptly instituted The interval in which successful resuscitation may be initiated varies with the degree of damage which was sustained prior to cessation of circulation

Immediate treatment

Initial measures to establish artificial ventilation and circulation are the same whether performed by physicians or lay rescuers and whether performed in a hospital or any other location Immediate recognition of the nature of the life threatening situation is the first step

Airway In most instances respiration stops before circulation Since any other measures will be ineffective in the absence of pulmonary ventilation respiration should always be checked first Movement of the chest or abdomen indicates that the victim is trying to breathe Even though breathing movements are noted the airway is obstructed if no air can be heard or felt moving in and out of the victim s nose and mouth

Natural soft tissue obstruction of the airway by a comatose patient s tongue can be corrected by stretching the soft tissues of the neck which are attached to the mandible In most unconscious patients maximal backward tilt of the head relieves obstruction If backward tilt of the head is not followed by free movement of air through the victim s mouth anterior displacement of the mandible should be combined with backward head tilt The jaw is lifted forward so that the lower teeth jut out in front of the upper teeth in the maximum prognathic position

Breathing If the victim is not making breathing movements the rescuer should take a deep breath open his mouth widely and after pinching the victim s nose to prevent leakage blow into his mouth with sufficient force to expand the victim s chest Unless expansion occurs the victim s lungs have not been ventilated In this event the victim s head and jaw should be repositioned and the rescuer should blow more forcefully If chest expansion is still not achieved the rescuer should quickly examine the victim s pharynx for vomitus or foreign material and remove it with his fingers suction or forceps Food lodged near the vocal cords is best loosened by repeated blows between the shoulder blades preferably with the victim inverted Prolonged manipulation must be avoided and inflation of the lungs must be accomplished as quickly as possible

After a few successful lung inflations the rescuer should feel for a pulse in one of the victim s carotid or femoral arteries If a pulse is felt it indicates that there is sufficient circulation to permit resuscitation by artificial ventilation alone If a pulse is not felt two situations are possible First the heart may be in cardiac arrest Second the heart may be beating so weakly that a pulse cannot be felt Skilled observers are usually not able to feel a carotid pulse when the systolic blood pressure falls below 60 mm Hg If a pulse is not felt the rescuer should give three or four more breaths and check again for a pulse In some instances when a weak circulation exists enough oxygen may be transported to reoxygenate the heart and restore circulation

Cardiac compression If a pul e is not felt after 30 seconds of ventilation artificial circulation must be started The heart occupies most of the space between the sternum and the vertebral column in the lower chest When the sternum is compressed toward the vertebral column blood is forced out of the heart into the arterial system When the sternum is released the normal elasticity of the chest wall causes it to rebound and during this period the heart fills with blood from the venous system Although the circulation produced in this fashion is of a lesser magnitude than normal *it is sufficient* to reoxygenate the arterial blood when combined with artificial ventilation Unfortunately it is usually not sufficient for adequate tissue perfusion so that the

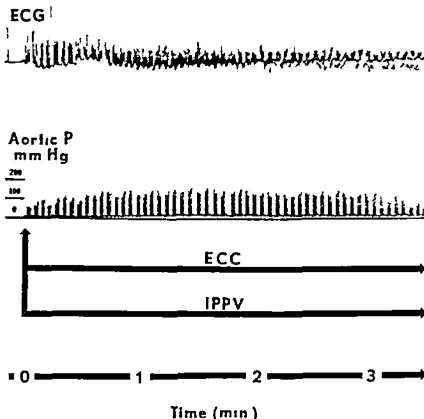


Fig 1 Unsuccessful attempt to resuscitate an asphyxiated dog without use of a vasoconstrictor drug Note that systolic pressures produced by external cardiac compression *(ECC)* are adequate but diastolic pressure does not exceed 10 mm Hg *IPPV* = intermittent positive pressure ventilation with air

emergency is not over when CPR is started It is most urgent to restore cardiac action at the earliest possible moment to prevent irreversible damage of the vital tissues

The principal function of circulation is to transport oxygen so that artificial ventilation and circulation must be used together The victim must be placed with his back resting on a firm surface His legs should be elevated to augment venous return to the heart and increase artificial cardiac output If two rescuers are present one should ventilate the lungs at a rate of 12 breaths/minute while the other compresses the sternum about 60 strokes/minute Each lung inflation should be followed by five sternal compressions at one second intervals Pressure should be applied with one hand on top of the other The heel of the lower hand is placed only in the midline over the lower half of the sternum If only one rescuer is present the best compromise is to deliver two or three breaths followed by 15 compressions of the sternum It ha[illegible]own that maintaining an equal ratio [illegible]mpression and relaxation on the sternum [illegible] important in maintaining cardiac output than is the rate of compression Judgment must be exercised to adjust the force of blowing to produce visible expansion of the victim s chest and of sternal compression to produce artificial pulsations in the carotid artery

Drugs Recommendations for the use of drugs in cardiac resuscitation are often obscure conflicting and based on inference from the actions of the agents under other circumstances However experimental evidence indicates that proper drug therapy greatly increases the effectiveness of resuscitation It must be emphasized that in the absence of effective artificial ventilation and circulation no pharmacological maneuvers can possibly correct cardiac arrest

The objectives of drug therapy during cardiac arrest are first to increase blood flow to the coronary arteries and second to minimize the adverse effects of metabolic acidosis which results from inadequate tissue perfusion

Epinephrine s value in cardiac resuscitation has been known since 1896 Because the drug has both potent inotropic and chronotropic effects on

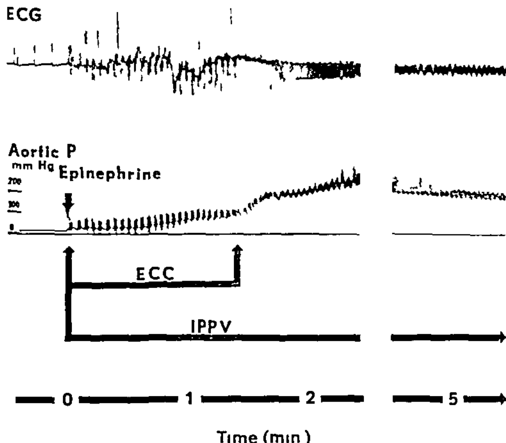


Fig 2 Successful resuscitation of an asphyxiated dog using external cardiac compression *(ECC)* and intermittent positive pressure ventilation with air *(IPPV)* Epinephrine 1 mg was given intravenously when resuscitation was started Note prompt rise in diastolic pressure and return of spontaneous circulation Arterial pH was 7 08 at the time of resuscitation

the beating heart and also produces intense peripheral vasoconstriction there has been confusion regarding its useful property in restarting an arrested heart As early as 1906 Crile and Dolley[11] noted the importance in cardiac resuscitation of securing coronary pressure of 30 to 40 mm Hg and felt that it usually was not possible to achieve this by cardiac massage alone without the use of epinephrine (Fig 1) Since that time it has been repeatedly demonstrated experimentally that epinephrine's value does not lie in its direct action on the heart Instead it increases peripheral vascular resistance transiently decreasing perfusion of most of the body but in the process increasing aortic diastolic pressure (Fig 2)[1] Since coronary blood flow occurs during diastole in either the spontaneously beating or arrested heart which is being compressed the result is increased coronary flow and myocardial reoxygenation In the most recent reexamination of this phenomenon it was found that alpha adrenergic blockade prevented resuscitation of animals with cardiac arrest while resuscitation of animals with beta receptor blockade was uniformly successful

Drugs which have their principal effect by cardiac stimulation such as isoproterenol or calcium salts may be useful in supporting circulation after the heart is restarted but are useless during the period of cardiac arrest On the other hand drugs which do not have epinephrine's cardiac stimulating effect but are potent peripheral vasoconstrictors such as phenylephrine 10 mg or methoxamine 20 mg (Fig 3) are as effective as epinephrine in restarting the arrested heart[1] In fact when peripheral resistance was increased by inflation of an abdominal binder during resuscitation of dogs there was an increase in aortic diastolic pressure (Fig 4) and resuscitation was as successful as when a peripheral vasoconstrictor drug was given and far more effective than when no drug therapy was used

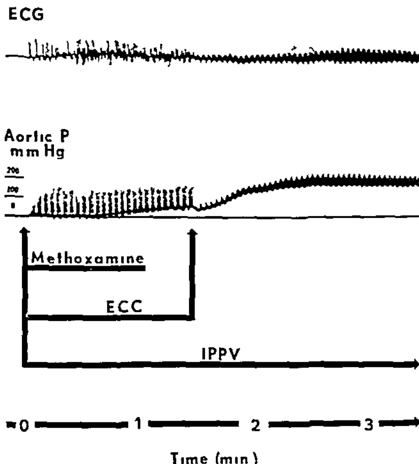


Fig 3 Successful resuscitation of an asphyxiated dog using external cardiac compression *(ECC)* and intermittent positive pressure ventilation with air *(IPPV)* Methoxamine 20 mg was given intravenously when resuscitation was started. Note prompt rise in diastolic pressure and return of spontaneous circulation

The vasoconstrictor effect is as important in resuscitation from ventricular fibrillation as it is in cardiac standstill In this situation myocardial reoxygenation accounts for the often described conversion of fine to coarse fibrillation which is necessary for successful electrical defibrillation When the two drugs were studied in resuscitation from ventricular fibrillation resuscitation employing epinephrine 1 mg prior to the countershock was significantly more effective than when no drug was used Methoxamine 20 mg was significantly more effective than epinephrine under these circumstances This may be attributable to the fact that methoxamine increases total coronary and subendocardial blood flow by peripheral and selective subepicardial alpha adrenergic vasoconstriction

There should be no delay in using an appropriate vasoconstrictor during resuscitation from either cardiac standstill or ventricular fibrillation and treatment of cardiac arrest is no time for homeopathic doses Since the useful action of the drug is on the peripheral circulation intracardiac injection is not advantageous over intravenous injection and is associated with the risk of pneumothorax or bleeding into the pericardium In fact when an endotracheal tube is in place and intravenous injection is not immediately possible the drugs may be diluted tenfold with water and given down the endotracheal tube This gives a response which is as quick and effective as either intracardiac or intravenous injection

When an intravenous route has not been established before cardiac arrest occurs it should be accomplished as soon as feasible for continued drug therapy Often the peripheral veins are collapsed and percutaneous venipuncture may be difficult or impossible If this is the case a rapid cutdown should be performed on a vein in one of the extremities Fortunately the superficial jugular is often distended or a femoral vein may be located medial to the pulsation caused by cardiac

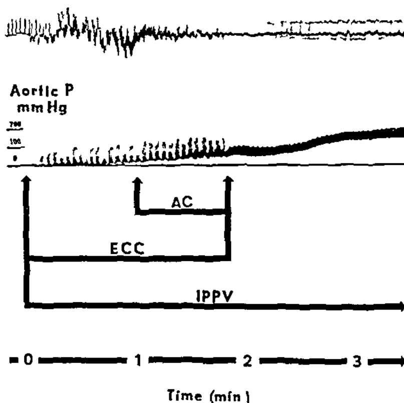


Fig 4 Successful resuscitation of an asphyxiated dog using external cardiac compression (ECC) and intermittent positive pressure ventilation with air (IPPV) Abdominal compression (AC) was produced by inflation of a binder one minute after resuscitation was started Note prompt rise in diastolic pressure and return of spontaneous circulation No dru therapy was employed

compression in the femoral artery making percutaneous venipuncture quick and easy Approaches to the subclavian and internal jugular veins should *not be attempted during cardiac* arrest since these routes necessitate interruption of CPR and are associated with complications which may lead to failure of resuscitation

It has been well established that in the absence of adequate tissue perfusion anaerobic metabolism results in production of lactic acid and other metabolites which cause severe metabolic acidosis During the period following the widespread adoption of CPR there were many advocates of the early use of sodium bicarbonate to correct this acidosis on the assumption that it would promote early restoration of cardiac function For several years it was common to observe the administration of large amounts of sodium bicarbonate while drugs of established value were neglected Even currently priority is given in the recommendations of the National Heart Association–National Research Council to administration of sodium bicarbonate before drugs demonstrated to be of value in restoring cardiac function This attitude was based on observations that administration of bicarbonate to animals before induction of cardiac arrest made them easier to resuscitate that acidotic animals had diminished response to catecholamines and that calves made hypotensive by infusion of hydrochloric acid could be restored by infusion of sodium bicarbonate These observations culminated in such recommendations as No time should be wasted in the first instance with adrenalin—and other drugs The appropriate treatment is the intravenous administration of 8 4% sodium bicarbonate solution

Subsequent investigation showed that sodium bicarbonate alone given during CPR did not promote return of cardiac contractility In fact accurate correction of metabolic acidosis was not feasible until cardiac resuscitation

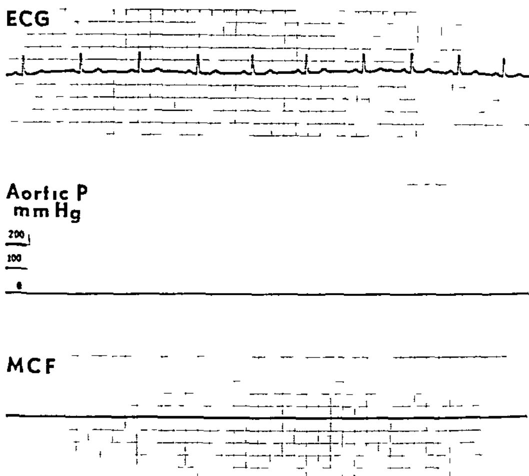


Fig 5 Simultaneous recordings of electrocardiographic activity absent aortic blood pressure and absent myocardial contractile force (MCF) recorded from a Walton Brodie strain gauge sutured to the left ventricle

successful and improved tissue perfusion mobilized acid metabolites sequestered in the tissues Administration of bicarbonate did not potentiate the effect of suboptimal doses of epinephrine while epinephrine 1 mg was found to be highly effective even in the presence of severe metabolic acidosis

Other experiments demonstrated that the susceptibility of the heart to development of ventricular fibrillation was increased in the presence of metabolic acidosis and that this could be corrected by administration of bicarbonate Variations in respiratory parameters had no such effects

In another study numerous physiological parameters were recorded during cardiac arrest and attempted resuscitation The most common derangement noted among the patients who could not be resuscitated and who were classified as having intractable cardiac arrest was metabolic alkalosis rather than acidosis From another institution it was reported that a hyperosmolal state considered incompatible with life was found in a series of patients who could not be resuscitated The hyperosmolal state was attributed directly to injection of hypertonic sodium bicarbonate Moreover sodium bicarbonate infusion resulted in a significant rise in arterial carbon dioxide tension which parallels the rise in pH

Is there a practical approach to the rational use of sodium bicarbonate in cardiac resuscitation? The principal value of sodium bicarbonate is to prevent metabolic acidosis from lowering the threshold of the heart to ventricular fibrillation Of itself bicarbonate will not promote early restoration of spontaneous cardiac activity while prompt and adequate doses of peripheral vasoconstrictor drugs will aid in restarting the heart Bicarbonate need not be given when cardiac arrest is known to have been of brief duration and pre-existing acidosis is unlikely Under most circumstances dosage must be empiric Fifty milliequivalents every five minutes during the period of actual cardiac arrest would seem safe

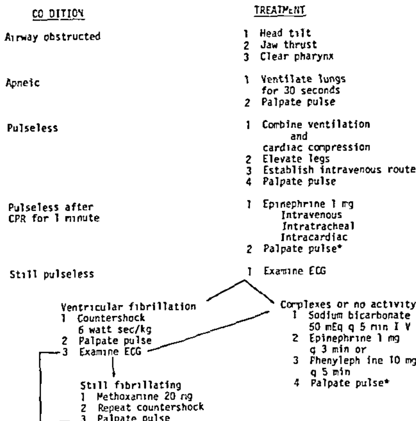


Fig 6 Algorithm for cardiopulmonary resuscitation

and adequate and deliberate hyperventilation of the patient should prevent carbon dioxide retention Arterial blood gas determinations should guide more precise dosage when continued therapy is indicated

Electrocardiography and countershock There are two functional types of cardiac arrest ventricular fibrillation and asystole and there are no external signs which permit differential diagnosis of the two conditions Consequently a reliable electrocardiograph or electrocardiographic oscilloscope is an essential item of equipment for definitive treatment of cardiac arrest

Ventricular fibrillation is a totally disorganized ineffective quivering of the heart muscle so that no cardiac output results Cardiac contraction is impossible because various portions of the myocardium are in different stages of depolarization simultaneous excitation of the entire myocardium being prevented by refractory areas Ventricular fibrillation is recognized by the totally disorganized formless wandering of the electrocardiographic baseline Prompt recognition is essential since the only practical method of correcting ventricular fibrillation is by electrical countershock Consequently a reliable external defibrillator is a second essential item of equipment for definitive cardiac resuscitation Currently most hospitals are equipped with direct current defibrillators which deliver a capacitor discharge of 100 to 400 watt seconds For patients weighing less than 50 kilograms the initial countershock should be about 6 watt seconds per kilogram and for patients weighing more than 50 kilograms the full output of the defibrillator should be used Each defibrillator must be tested to determine the percentage of indicated energy that is delivered

The electrocardiographic pattern of asystole may be of two kinds There may be no electrical

activity at all so that only a straight line is recorded or not uncommonly ventricular complexes which often are relatively normal in appearance may be recorded while there is a total absence of cardiac output No palpable pulses or blood pressure can be detected Electrocardiographic activity does not indicate myocardial contractility (Fig 5) Whether electrocardiographic complexes are recorded or not does not modify either the treatment or the prognosis Often asystole converts to ventricular fibrillation during resuscitation as partial reoxygenation of the myocardium causes differing areas of electrical potential Therefore constant monitoring of the pulse and electrocardiogram are essential and one should not assume that the heart is beating because of the appearance of the electrocardiogram Countershock is useful in resuscitation only when ventricular fibrillation is known to be present Shocks applied to the asystolic heart accomplish nothing and waste time Electric current applied to the anoxic heart is ineffective so that attempts at electrical pacing during most cases of cardiac arrest are useless Countershocking frequently converts ventricular fibrillation to asystole with or without ventricular complexes If a pulse cannot be felt after countershocking CPR and drug therapy should be continued until a pulse can be palpated

For those who prefer the algorithmic approach to emergency situations Fig 6 outlines an effective protocol to avoid confusion and delay in CPR

Support after resuscitation

Detailed discussion of the many variables of supportive care after resuscitation from cardiac arrest is far beyond the scope of this paper Depending on the duration of the ischemic anoxic episode there may be no or extensive multiple organ system failure Circulation requires moment to moment monitoring and the use of appropriate cardiac inotropes calcium salts antiarrhythmics and other agents may be needed Respiratory support should be continued through the period of circulatory inadequacy and until objective evidence indicates that it is no longer necessary Premature cessation of respiratory support may result in recurring hypoxia and circulatory arrest If the patient is obtunded specific measures aimed at cerebral preservation are indicated and a major breakthrough in our understanding of appropriate management of this organ system is currently occurring Observation of the patient's level of consciousness and reflex activity provide the best prognostic indices to the ultimate success of the resuscitative effort

Common pitfalls

Observations during 20 years of teaching and supervising resuscitation programs in several major medical centers indicate that there are a number of errors in judgment which often jeopardize the successful outcome of resuscitation attempts even in institutions where the level of training and patient care is high

Records of the Cardiopulmonary Resuscitation Committee of the Medical University of South Carolina Hospital show that over 80% of the episodes of cardiac arrest occurring in that institution are due to impaired ventilation resulting in profound hypoxemia or asphyxia Primary cardiac arrests are relatively uncommon in most general hospitals and those which occur are most often related to myocardial infarction and are managed under the specialized conditions of Coronary Care Units

Many potentially successful resuscitative attempts fail because the management of cardiac arrest is confused with the treatment of shock or the life threatening arrhythmias Cardiac arrest is a distinct pathophysiological state which must be managed in a rapid organized fashion as already described if resuscitation is to be *effective* Often the urgency of restoring effective spontaneous cardiac function is not recognized The emergency is not over when resuscitation is started

In the hospital environment there is a tendency toward unnecessary use of equipment Use of even simple devices such as pharyngeal airways requires additional skill and judgment by the rescuer and often introduces avoidable complications The self inflating bag mask units which are used to avoid direct oral contact with the victim deliver very limited tidal volumes compared to mouth to mouth resuscitation and require considerable manual dexterity of the rescuer A happy compromise which is often forgotten is to apply the mask to the victim's face using both hands to maintain mask fit and head position and to perform mouth to mask ventilation Ill advised or clumsy attempts at tracheal intubation

count for many failures The principal advan ge of intubation is to prevent aspiration if gurgitation occurs Unskilled rescuers should ot attempt the maneuver since they usually recipitate the complication they are trying to revent Even skilled endoscopists should carry ut preliminary ventilation before intubation

Most patients who become seriously hypoxic evelop bradycardia This is due to myocardial ypoxia rather than to vagal reflex The appro riate drug is oxygen not atropine If use of tropine or cardiac inotropic agents increases the eart rate in the absence of improved oxygena on cardiac arrest occurs more quickly as the esult of increased myocardial oxygen consump on

Unnecessary interruptions of CPR to intubate he trachea or because of preoccupation with the lectrocardiographic pattern are to be avoided During the period of cardiac arrest the only lectrocardiographic pattern which alters treat nent is ventricular fibrillation In this case coun ershock is indicated Often inadequate doses of urrent are used initially with progressive ncreases as repeated shocks are needed The esult is delay in restoration of spontaneous irculation and prolonged tissue hypoxia

If a sound and organized approach to cardio espiratory emergencies becomes ingrained resus itation can be carried out swiftly without hesita ion and inappropriate improvisation The results an be rewarding

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Clinical pharmacology of the new beta-adrenergic blocking drugs Part 8 Self-poisoning with beta-adrenoceptor blocking agents recognition and management

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Beta adrenoceptor blocking drugs are now widely prescribed for a multitude of indications in clinical medicine[1] They are extensively used either alone or in combination with other agents to treat cardiac arrhythmias of ventricular or supraventricular origin angina pectoris obstructive cardiomyopathies essential hypertension and thyrotoxicosis[2] Beta adrenoceptor blocking drugs may also be of benefit in some patients with hyperkinetic heart syndromes migraine headache essential tremor anxiety psychoses acne vulgaris alcohol and narcotic withdrawal and septic shock

The beta adrenoceptor blocking drugs have many associated adverse effects when used in the therapeutic dose range, which were described in a previous article With the growing application of these drugs in clinical practice cases of attempted suicide and accidental overdosage are being reported The clinical manifestations of massive intoxication in humans have not been well appreciated Moreover the management of patients with overdosage is a subject of controversy Variations in the pharmacological properties of the different beta adrenoceptor blockers (cardioselectivity partial agonist effect) affect their therapeutic actions and adverse effects These individual differences may influence the clinical features of serious overdosage

In this report we will review[3] our own experiences in four patients with propranolol intoxication the world experience with beta adrenoceptor blocking drug overdosage[3] and the currently recommended therapeutic modalities for this problem

Case reports

Four cases of massive propranolol intoxication seen at our institution are described below Data from these patients are summarized in Table I

Case 1 A 17 year old previously healthy black female was brought to the emergency room 2 hours after ingesting 30 to 40 of her mother's 40 mg propranolol tablets (1 200 to 1 600 mg) in a suicide attempt Within 90 minutes of ingestion she had become stuporous and experienced generalized seizures lasting several minutes She was comatose with only avoidance responses to painful stimuli on arrival at the hospital Blood pressure was unobtainable heart rate 50 per minute and respiratory rate 20 per minute with shallow chest excursions Pupils were 4 mm equal and reactive to light There were rhonchi at both bases The extremities were cool but not cyanotic tendon reflexes were moderately active and symmetrical Minutes after arriving at the hospital the patient had a generalized tonic clonic seizure which responded promptly to 5 mg

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of intravenous diazepam She was then given two doses of 0 06 mg of epinephrine intravenously resulting in an increase of the heart rate to 70 per minute and blood pressure to 90/50 At the time of admission serum sodium concentration was 138 mEq/L potassium 4 5 mEq/L calcium 8 1 mEq/L bicarbonate 21 mEq/L chloride 100 mEq/L and glucose 136 mg/dl Arterial pH was 7 30 pCO 26 torr and pO 121 torr Routine toxicological screening showed the presence of a barbiturate in the first of two specimens of gastric contents however urine screening was negative The patient had no prior history of seizures or cardiovascular disease Her level of consciousness improved over the next several hours and the day after admission she was alert and oriented with a completely normal neurological examination Serum propranolol levels were not drawn immediately on arrival but 24 hours later the serum propranolol measured spectrofluorometrically was 449 ng/ml decreasing to 19 ng/ml at 48 hours after admission and to nondetectable levels at 96 hours An ECG taken upon admission (Fig 1) showed regular sinus rhythm first degree heart block and an intraventricular conduction defect Twenty four hours later the ECG was normal An EEG performed on the eighth hospital day was normal

Case 2 A 25 year old woman came to the Bronx Municipal Hospital Emergency Room thirty minutes after ingesting two handfuls of 40 mg propranolol tablets in a suicide attempt She was alert and agitated had a pulse of 116 per minute and a blood pressure of 150/100 The patient received 30 c c of Ipecac syrup and several minutes later she vomited green pill fragments Subsequently she suffered a grand mal seizure At that point her blood pressure was unobtainable and her pulse was 50 per minute The patient was given one mg of atropine two mg of isoproterenol and four mg of glucagon intravenously and subsequently was begun on continuous infusions of isoproterenol glucagon and dopamine with a resultant increase in her pulse to 80/minute and blood pressure to 80/50 Despite injection of phenobarbital 240 mg intravenously she then experienced two more generalized seizures each lasting only seconds Physical examination shortly thereafter was remarkable for a lethargic but arousable woman whose pupils were each 6 mm and reactive to light The

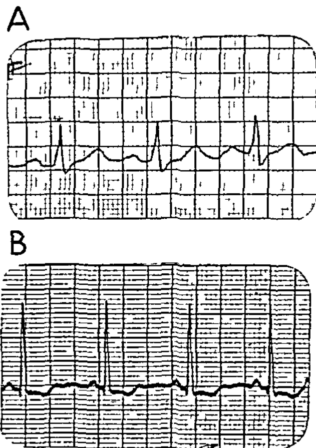


Fig 1 Electrocardiogram (Lead III) of patient with propranolol overdose (Case No 1) The upper tracing (*A*) was taken at the time of hospital admission and shows regular sinus rhythm first degree heart block (prolonged PR interval) and an intraventricular conduction defect The lower tracing (*B*) (Lead III) taken 24 hours later with another electrocardiograph shows non specific ST segment depression and normalization of conduction intervals

remainder of the examination was unremarkable At the time of admission serum sodium concentration was 139 mEq/L potassium 3 5 mEq/L bicarbonates 15 mEq/L calcium 9 7 mg/dl chloride 100 mEq/L and glucose 207 mg/dl Arterial blood pH was 7 41 pCO_2 20 torr and pO 75 torr Toxicological screening of the urine was negative for any drugs Serum propranolol levels done spectrofluorometrically were 2 300 ng/ml on admission 800 ng/ml five hours later and 300 ng/ml 24 hours later An ECG taken upon admission revealed normal sinus rhythm with a QRS duration of 0 12 sec Twenty four hours after admission the ECG was normal The patient made an uneventful recovery

Table I Summary of 4 patients with propranolol overdosage treated at the Bronx Municipal Hospital Center

No	Age	Sex	Plasma level (ng/ml)	Estimated ingestion (mg)	Heart rate (beats/min)	Blood pressure (mm Hg)	Level of consciousness	Convulsions (yes no)
1	17	F	449	1,200 1 600	50	Unobtainable	Comatose	Yes
2	25	F	2,300	?	116 → 50	150/100 → Unobtainable	Alert Agitated	Yes
3	19	F	2,800	1 600	80 → 50	130/80 → 90/60	Comatose	Yes
4	59	M	1 800	2 000	50	120/70	Semi delirious	No

Obtained 24 hours after admission
Abbreviations IVCD = intraventricular conduction defect

Case 3 A 19 year old female with a history of paroxysmal atrial tachycardia ingested 80 20 mg tablets of propranolol in a suicide attempt and was brought to the emergency room one hour later in a semiconscious state She had a pulse rate of 80 and a blood pressure of 130/80 A nasogastric tube was inserted for gastric lavage with recovery of pill fragments and activated charcoal was given Fifteen minutes later she became delirious then unresponsive and experienced a grand mal seizure Her blood pressure at the time was 90/60 and her heart rate 50 per minute The patient was treated with 1 mg of intravenous atropine and 2 mg of intravenous isoproterenol with no response in heart rate and blood pressure Intravenous valium was given after which the seizures stopped An infusion of isoproterenol and glucagon were begun which resulted in an increase in her blood pressure to 110 60 and her pulse rate to 70 per minute Physical examination revealed a lethargic but arousable woman with reactive pupils Chest and cardiac examinations were unremarkable Her admission serum sodium was 139 mEq/L potassium 3.8 mEq L bicarbonate 17 mEq/L calcium 9.4 mg/dl chloride 99 mEq/L and glucose 135 mg/dl Toxicological screening was negative for drugs An initial plasma propranolol level was 2800 ng/ml 1 100 ng/ml five hours later and 270 ng ml 24 hours later An ECG taken upon admission demonstrated first degree heart block with a PR interval of 0 24 sec and a QRS duration of 0 10 sec Twelve hours later her ECG was normal with a QRS duration of 06 sec Her chest roentgenogram upon admission showed no evidence of left ventricular dilation or pulmonary congestion Subsequent neurological examinations were unremarkable and the patient made an uneventful recovery

Case 4 A 59 year old white male with long standing hypertension but no other known cardiac disease ingested approximately 50 of his 40 mg propranolol tablets in a suicide attempt He was brought to the emergency room in acute pulmonary edema cyanotic and semi delerious Upon arrival in the emergency room he was found to have a blood pressure of 120/70 and a weak pulse at a rate of 50 per minute He was treated with oxygen rotating tourniquets and 80 mg of intravenous furosemide The chest roentgenogram revealed fluffy alveolar infiltrates and cardiomegaly The ECG demonstrated first degree heart block (PR interval of 0 24 sec) and a heart rate of 50 per minute There was QRS widening of 0 11 sec

The patient received 1 mg of intravenous atropine and 1 mg isoproterenol with no increment in heart rate A transvenous pacemaker was inserted with the rate set at 70 per minute and 10 mg of glucagon was injected intravenously The patient responded within 10 to 15 minutes with improvement in his cardiovascular status and was maintained on an isoproterenol and glucagon drip for 8 hours The pacemaker was removed after 24

Pre antidote				Treatment
Congestive heart failure (yes no)	Bronchospasm (yes no)	Blood sugar (mg /dl)	ECG findings	
No	No	136	Regular rhythm 1st heart block IVCD	Diazepam epinephrine
No	No	207	NSR IVCD	Atropine phenobarbital isoproterenol glucagon and dopamine
No	No	135	Regular rhythm 1st heart block IVCD	Diazepam atropine glucagon isoproterenol,
Yes	No	150	Regular rhythm 1st heart block IVCD	Pacemaker oxygen diuretics atropine glucagon isoproterenol

hours The subsequent ECG revealed a heart rate of 76 per minute with normal PR and QRS durations A plasma propranolol level done at the time of admission was 1 800 ng /ml An echocardiogram 72 hours after admission revealed left ventricular hypertrophy and a slightly diminished ejection fraction The patient was discharged following psychiatric evaluation with no *further cardiac disorder*

Comment

These four cases of propranolol self poisoning reveal many of the features of massive beta adrenoceptor blocker intoxication hypotension bradycardia prolonged atrioventricular conduction times An unusual feature was that three of the patients had grand mal seizure activity In only one previous instance of massive overdosage with propranolol have generalized seizures been described Drug induced hypoglycemia and other metabolic causes of seizures were ruled out Although cerebral hypoperfusion may have contributed the second and third patient suffered convulsions despite an adequate blood pressure The seizures were responsive to intravenous diazepam in two patients and unresponsive to phenobarbital in one patient After recovery in all patients there was no evidence of neurological disease

All four patients had significant changes in their levels of consciousness ranging from frank coma to delirium Propranolol is a beta adrenoceptor blocking agent which is not cardioselective and has membrane depressant action (quinidine or local anesthetic property) The drug is extremely lipid soluble and rapidly crosses the blood brain barrier to concentrate in brain tissue The membrane depressant effect of propranolol is not important in the usual therapeutic dose range however this might become important with massive intoxications The seizures and change in mental status may be similar to effects seen with lidocaine another lipophilic local anesthetic drug

Another unusual presentation was the widening of the QRS complex of the electrocardiogram evidence of an intraventricular conduction defect This finding is not a feature of the propranolol effect in usual therapeutic doses It may be a result of the quinidine or membrane depressant effect of propranolol which is seen with massive doses

No patient had definite evidence of bronchospasm or developed hypoglycemia Patient No 4 developed acute pulmonary edema following a 2 gm propranolol ingestion Higher doses have been given to patients with normal hearts over 24 hours without evidence of left ventricular decompensation[1] On the other hand patients with occult myocardiopathy have gone into pulmonary edema with as little as 40 mg of propranolol It may be that patient No 4 had an occult hypertensive cardiomyopathy which only manifested itself after the self poisoning episode

All patients responded to therapy and recovered from their overdosage without sequelae

Table II Summary of pharmacological properties of beta adrenoceptor blocking drugs[11,12]

Drug	Synonyms	Cardio selectivity	Partial agonist activity	Membrane stabilizing activity	Usual therapeutic dose range (mg/day)	Beta blocking plasma concentrations
Acebutolol	Sectral (M & B 17 803A	+	+	+	400 800	0.2-2 μg/mL
Alprenolol	H56/26 Aptin Betaptin Betacard	0	++	+	200-800	50-100 ng/mL
Atenolol	ICI66082 Tenormin	+	0	0	100-400	0.2-0.5 μg/mL
Metoprolol	H93/26 Lopressor Betaloc	+	0	±	100-800	50-100 ng/mL
Oxprenolol	Ciba 39089 Ba Trasicor	0	++	+	40-360	80-100 ng/mL
Pindolol	LB-46 Visken	0	+++	+	2.5 30	50-150 ng/mL
Practolol	ICI50172 Eraldin	+	++	0	25-800	1.5-5 μg/ml
Propranolol	ICI45520 Inderal Avlocardin	0	0	++	80 480	50-100 ng/ml
Sotalol	MJ1999 Betacardone Sotacor	0	0	0	80-480	0.5-4 μg/mL
Timolol	MK 950 Blocadren	0	±	0	5-40	5-10 ng/mL

Review of the world experience with beta adrenoceptor blocker self poisoning

Variations in pharmacological properties of the different beta adrenoceptor blocking agents (Table II) affect their therapeutic action and predictable side effects. These differences may influence the clinical presentation of massive overdosage. The reported cases of beta adrenoceptor self poisoning are reviewed below and are summarized in Table III.

Acebutolol (cardioselective partial agonist activity membrane depressant). There have been no reports of self poisoning with acebutolol to date.

Alprenolol (non cardioselective partial agonist activity membrane depressant). One fatal case of alprenolol self poisoning has been reported in a 32 year old female who ingested 12.8 gm of drug (approximately 64 200 mg tablets). She presented with hypotension coma and had a respiratory arrest. Despite the supportive measures the patient eventually developed asystole and died. Her postmortem alprenolol blood level was 1 300 ng ml.

Atenolol (cardioselective no partial agonist activity or membrane depressant effects). A 24 year-old female who was receiving atenolol for treatment of hypertension ingested 1 200 mg of drug six times greater than the therapeutic dose in a suicide attempt.[14] She was admitted to the hospital 2 to 3 hours later in good condition. Her pulse rate was 80 beats per minute with a recumbent blood pressure of 150/110 mm Hg. There were no signs of cardiac decompensation and the ECG was normal. She was closely monitored over the ensuing days during which time her pulse rate varied between 66 to 60 beats per minute in sinus rhythm. Her blood pressure was 190/120 mm Hg 5 days after ingestion. The clinical course was uncomplicated.

Metoprolol (cardioselective no partial agonist activity weak membrane depressant activity). Two cases of non fatal metoprolol intoxication have been reported.

1. A 19 year old male was admitted to the hospital after having ingested 200 50 mg tablet (10 000 mg).[15] Upon arrival at the hospital he was conscious with peripheral cyanosis weak heart sounds and an unmeasurable blood pressure. The electrocardiogram revealed sinus rhythm of 60 to 70 per minute with normal atrioventricular conduction ST segments and T waves. He was treated with metaraminol and glucagon following gastric lavage. Two hours after admission the plasma level of the drug was 12 200 ng/ml. Complete recovery occurred within 12 hours without signs of cardiovascular depression.

2. A 17 year old daughter of a hypertensive

Elimination half life (h)	*Lipid solubility*	*Urinary recovery of unchanged drug (% of dose)*
about 8	–	–
2 3	strong	<1
6-9	–	40
3-4	weak	3
2	weak	–
3-4	weak	40
6-8	weak	>90
3.5-6	strong	<1
5-13	–	60
4-5	–	90

patient ingested over 10 gm of metoprolol combined with alcohol and diazepam Upon hospital admission one hour later she was found to be conscious but very drowsy There was no cyanosis and respirations were not affected Her blood pressure was 80/60 mm Hg and her radial pulse was 72 per minute and regular Heart sounds and pupillary reaction were normal A resting electrocardiogram on admission showed no pathological findings She was admitted to the intensive care unit and had normal sinus rhythm throughout Treatment consisted of fluids Blood pressure rose slowly during the course of the first 3 hours to 90/80 mm Hg and later to the patient s normal level of 115/70 mm Hg Pulse rate varied during monitoring between 60 and 85 per minute Twelve hours after admission the patient was up and about in good condition The concentration of metoprolol in plasma was 13 000 ng/ml measured 11 hours after ingestion The patient made an uneventful recovery

Oxprenolol (non cardioselective partial agonist activity membrane depressant) Five cases of oxprenolol overdosage have been reported with two fatalities

1 A 29 year old male committed suicide by ingesting over 300 mg of oxprenolol after drinking 11 pints of beer[1]

2. A 57 year old female ingested 112 40 mg tablets of oxprenolol (4 480 mg) She was brought to the emergency department 20 minutes later in coma She was cold and clammy and had central cyanosis Her pulse was not palpable and her blood pressure was unrecordable Heart sounds were soft with a ventricular rate of 36 per minute and she had bibasilar rales The ECG revealed an idioventricular rhythm at a rate of 36 External cardiac massage and assisted respiration procedures were carried out There was no response in pulse rate to intravenous atropine and isoproterenol A transvenous pacing catheter could not capture the ventricle The patient died in asystole 1 hour after arrival in the hospital An autopsy revealed no gross structural abnormality of the circulatory system The postmortem plasma drug level was approximately 400 ng/ml.

3 A 62 year old male ingested a large amount of oxprenolol and diazepam He was brought to the hospital pulseless with cold cyanotic extremities after being supported by the ambulance crew The admission ECG revealed asystole After 35 minutes of resucitative efforts which included intravenous isoproterenol and epinephrine infusions a slow sinus rhythm of 32 was established. This increased to 68 beats per minute after 0 6 mg of intravenous atropine and respirations also returned Systolic blood pressure did not increase over 30 mm Hg Further epinephrine by continuous infusion had no effect on heart rate or blood pressure over 1½ hours Glucagon 10 mg intravenously produced an arterial blood pressure of 150 mm Hg within 60 seconds and an improvement in peripheral circulation As the cardiovascular state improved severe bronchospasm developed which was treated successfully with intravenous terbutaline A continuous infusion of glucagon 2 mg hourly was given over the next 5 hours and improvement continued after its withdrawal The patient was eventually discharged after an uncomplicated recovery The oxprenolol plasma level was 3 100 ng/ml

4 A 39 year old female ingested 3 gm of oxprenolol After arrival at the emergency unit she had a respiratory arrest and a mild generalized convulsion The blood pressure was unrecordable and the pulse very feeble but spontaneous respirations returned and the cardiac monitor showed sinus rhythm with a rate of 60 per minute Two further brief convulsions occurred. Following transfer to the intensive care unit she had a cardiorespiratory arrest with the monitor show

Table III

Drug	Pt. No	Age	Sex	Pre-antidote: Estimated ingested dose (mg.)	Other drugs	Plasma level (ng/mL)	Heart rate beats/min	Blood pressure (mm. Hg)	Level of consciousness
Alprenolol	1	32	f	12,800	0	1,300		60 systolic	coma
Atenolol	1	24	f	1,200	0		80	150/110	alert
Metoprolol	1	19	m	10 000	0	12,200	60-72	not measurable	alert
	2	17	f	10 000	alcohol, diazepam	13,100	72	80/60	drowsy
Oxprenolol	2	57	f	4 480	0	400	36	not measurable	coma
	3	62	m	?	diazepam	3 100	0	not measurable	coma
	4	39	f	3 000	0		unobtainable	not measurable	coma
Pindolol	1	38	f	500	0	1,500	80	240/140	alert
	2	24	f	250	diazepam	660	110	130/80	coma
Practolol	1	39	m	9 000	0	58,600	70	90/60	alert
	2	39	f	5 000	0		100	110/60	alert
Propranolol	1	45	m	2,000	0		80	120 systolic	alert
	2	35	f		0	28 000			
	3	34	f	6 000	alcohol	14 000			
	4	38	f		codeine	16 000			
	5	22	m	4,000	0		50	110/70	alert
	6	37	f	800	diazepam, imipramine		50	60 systolic	
		24	f	1 000	alcohol		40 → asystole	unobtainable	coma
	8	41	m	5 100	? alcohol		50 → asystole	unobtainable	coma
	9	65	m	800	0	1 536	50	unobtainable	coma
	10		m	150	0		60	130 systolic	coma
	11	3	f	150	0		120	125/75	drowsy

Pre antidote							
Convulsions	Blood Sugar	Congestive heart failure (yes no)	Bronchospasm (yes no)	ECG	Treatment	Result	Reference
					supportive	Death	13
0		no	no	normal	supportive	Recovery	14
0		yes	no	normal	gastric lavage furosemide metaraminol glucagon	Recovery	15
0			no	normal	supportive	Recovery	16
0		yes	no	idioventricular rhythm	unresponsive to atropine isoproterenol pacemaker	Death	18
0		no	yes	asystole sinus bradycardia	unresponsive to atropine epinephrine responded to glucagon bronchospasm treated with terbutaline	Recovery	19
yes		no	no	bradycardia rate = 20	atropine isoproterenol, epinephrine pacemaker	Recovery	20
0		no	no	normal	none	Recovery	22
0	normal	yes	no	sinus tachycardia IVCD (QRS 11/ sec	fluids	Recovery	23
0		no	no	normal	supportive	Recovery	24
0		yes	no	LBBB	supportive	Recovery	25
0		no		normal	supportive	Recovery	26
					none	Death	27
					none	Death	28
					none	Death	29
0	normal	?		bradycardia rate = 42, transient atrioventricular block	atropine epinephrine	Recovery	30
0		yes			unresponsive to isoproterenol responded to glucagon	Recovery	31
0		?	yes	asystole	unresponsive to atropine responded to epinephrine	Recovery	32
yes		?		bradycardia then asystole	epinephrine isoproterenol, pacemaker	Recovery	7
0		?		1st AV block RBBB	isoproterenol	Recovery	33
?	14 mg/dl	no		sinus bradycardia atrioventricular block	glucose	Recovery	34
0	50 mg/dl	no		normal	glucose	Recovery	34

ing a bradycardia of 20 She was artificially ventilated and external cardiac massage was maintained for 2 hours She received atropine epinephrine (intra cardiac and intravenous) isoproterenol and sodium bicarbonate A pacemaker was inserted with 100% capture After 2 hours the blood pressure obtained was 130/100 mm Hg and she reverted to a sinus rhythm of 80 beats per minute Within 48 hours she was fully conscious and after 72 hours assisted ventilation was discontinued She made a full recovery

5 A 67 year old male ingested 30 80 mg oxprenolol tablets (2 400 mg) along with 25 thiazide potassium (navidrex K) tablets ' The major problem in his clinical presentation was hyperkalemia The oxprenolol may have delayed the normal excretion of potassium by lowering cardiac output and blood pressure The patient made an uneventful recovery following supportive measures

Pindolol (non cardioselective partial agonist activity weak membrane depressant) Two uncomplicated cases of pindolol self poisoning have been reported

1 A 38 year old female ingested 500 mg of pindolol in a suicide attempt [2] She had been receiving 30 to 40 mg of pindolol for treatment of hypertension She presented 5 hours after the massive ingestion with a blood pressure of 240/140 and a pulse rate of 80 per minute Her electrocardiogram was normal and she remained alert and cooperative Her plasma pindolol level was 1 500 ng /ml There were no further complications

2 A 24 year old female ingested 250 mg of pindolol along with 150 mg of diazepam [21] She presented the following morning in coma with a blood pressure of 80 mm Hg and a pulse of 110 beats per minute After infusion of fluids her blood pressure came up to 130 mm Hg The electrocardiogram revealed a sinus rhythm of 110 with a QRS duration of 0 11 sec The blood sugar was normal and pulmonary congestion was noted on the chest roentgenogram Twenty hours later the QRS duration on the electrocardiogram was 0 06 sec and the chest roentgenogram was normal The plasma pindolol level was 660 ng / ml and the patient made an uneventful recovery

Practolol (cardioselective partial agonist activity no membrane effec) Two non fatal cases of practolol self poisoning have been reported

1 A 39 year old male with mitral valve disease ingested 9 gm of practolol ' He had been taking 400 mg daily for arrhythmias Three hours after the massive ingestion he was taken to the hospital where his heart rate was 70 beats per minute and the blood pressure 90/70 mm Hg There were no changes in his level of consciousness and no signs of cardiac decompensation Over the next 2 hours his blood pressure rose to its usual level The plasma level was 58 6 μg/ml The patient s course was uncomplicated

2 A 39 year old female with mitral stenosis ingested 5 000 mg of practolol and presented with signs of mild congestive heart failure Her blood pressure was 110/60 and the heart rate 100 per minute There was intermittent blockage of the left bundle branch She made an uneventful recovery with resolution of the conduction defect

Propranolol (non cardioselective membrane depressant no partial agonist effect) In addition to our four cases of propranolol intoxication 11 other well documented cases have been reported with three fatalities The large experience with propranolol intoxication reflects its wide use in clinical practice

1 Wermut and Wojcicki reported a case of a 45 year old man who ingested 2 000 mg of propranolol in a suicide attempt He arrived at the hospital 2 hours later in good condition Plasma levels were not measured His heart rate was 80 beats per minute with a normal pulse contour, and his systolic blood pressure was 120 mm Hg The electrocardiogram showed normal sinus rhythm and his course was uncomplicated

2 A 35 year old female with a past history of psychiatric illness was found dead in her living room chair [2] Toxicological studies revealed a propranolol plasma level of 28 000 ng /ml and 600 mg of ingested drug remained in her stomach An exact cardiovascular cause for her death was not determined

3 A 34 year old female was found dead in bed having allegedly swallowed 6 gm of propranolol with a large amount of alcohol [28] The plasma propranolol level was 14 000 ng /ml and there was a massive concentration of drug in the brain An exact anatomical cause for death was not determined

4 A 38 year old schizophrenic female was found dead in bed having ingested an unknown amount of propranolol and codeine The plasma level of propranolol was 16 000 ng /ml An autop

sy revealed no significant gross pathological findings

5 A 22 year old male ingested 4 gm of propranolol in a suicide attempt[3] The blood pressure was 110/70 Sinus bradycardia ranged from 50 to 42 per minute and did not change with injections of epinephrine The heart rate increased somewhat after atropine There was no evidence of impaired atrioventricular conduction Hypoglycemia was not observed and the outcome was favorable

6 A 37 year old female attempted suicide with a mixed overdose of imipramine and 800 mg of propranolol[31] She presented in the emergency room cyanotic cold with marked distention of the neck veins The pulse rate was 50 and regular and the systolic blood pressure was 60 mm Hg She was unresponsive to an isoproterenol infusion but responded dramatically to 10 mg of glucagon intravenously The blood pressure rose to 95 mm Hg and the pulse rate to 70 beats per minute Marked improvement was also observed in peripheral perfusion and the degree of neck vein distention She had an uncomplicated recovery

7 A 24 year old female ingested 1 000 mg of propranolol with beer and whiskey[1] Two hours later she was admitted to the hospital with a pulse rate of 35 to 40 per minute and no blood pressure Rhonchi were heard over the lung fields Atropine was given intravenously but asystole developed Cardiorespiratory resuscitative efforts were begun and the patient responded to intracardiac epinephrine The patient s course thereafter was uncomplicated Plasma drug levels were not measured

8 A 41 year old male with a history of chronic alcoholism ingested 5 1 gm of propranolol He arrived in the emergency room 2 hours later and was found to be comatose and cyanotic with a pulse rate of 50 beats per minute The blood pressure was unobtainable and he experienced intermittent generalized convulsions The ECG showed a bradycardia without identifiable P waves He developed asystole and required intensive supportive efforts and therapy which included 115 mg of isoproterenol over 2½ days a transvenous pacemaker and intravenous epinephrine He remained in a coma for 18 hours and eventually made an uneventful recovery after 65 hours on an isoproterenol drip infusion Plasma levels were not measured

9 A 65 year old male ingested 800 mg of propranolol Two hours later he presented in coma with respiratory compromise The blood pressure was unobtainable and the pulse rate was 50 beats per minute The ECG demonstrated first degree heart block and right bundle branch block He responded to intravenous isoproterenol with a normalization of blood pressure ECG and heart rate Plasma renin activity was severely depressed during the acute intoxication and rose briskly as the drug effect wore off Plasma propranolol level was 1 536 ng/ml The patient s ultimate course was unremarkable

10 and 11 Propranolol induced hypoglycemia was seen in two healthy siblings a boy aged 20 months and a 3 year old girl who ingested 150 mg between them[4] The boy presented in stupor with a systolic blood pressure of 130 mm Hg and a pulse rate of 60 beats per minute The ECG showed sinus rhythm and periodic second degree atrioventricular block The plasma glucose was 14 mg/100 cc He responded to intravenous glucose with a dramatic improvement in his level of consciousness The electrocardiogram reverted to normal after three days The girl presented with drowsiness and diaphoresis Her blood glucose was 50 mg/100 ml The ECG pulse rate and blood pressure were normal She rapidly recovered after milk and sugar by mouth Ten days after admission an oral glucose tolerance test was performed in both children which was within normal limits

Sotalol (no cardioselectivity no partial agonist effect no membrane depressant action) and *Timolol* (weak partial agonist activity) There have been no reported cases of serious overdosage with these two agents

Discussion

Self poisoning with beta adrenoceptor blocking drugs is uncommon but is being reported with increasing frequency as the therapeutic indications for these agents continue to grow[6] The main clinical features of massive overdosage include bradycardia hypotension low cardiac output cardiac failure and cardiogenic shock[6] Bronchospasm may also occur and respiratory depression can develop perhaps as a result of severe circulatory impairment or from a central drug effect In severe intoxications the myocardium may become relatively refractory to pharmacological and electrical stimulation and death occurs in asystole[6]

Pharmacology When properly administered the beta adrenoceptor blocking drugs are rela

tively safe with a wide margin between therapeutic and toxic dose levels[31] However patients vary in their sensitivity to these drugs Some patients have tolerated therapeutic doses of up to 4 gm of propranolol daily[1] and deliberate over dosage of both practolol[34,5] and propranolol[6] without serious adverse effects Conversely circulatory collapse may occur in patients with pre existing cardiac failure when sympathetic drive is inhibited by even a small dose of a beta adrenoceptor antagonist

Variations in the pharmacological properties of the different beta adrenoceptor blocking agents (partial agonist activity cardioselectivity membrane depressant action lipid solubility) affect their therapeutic actions and adverse effects[5] These individual differences may influence the clinical features in serious overdosage In the therapeutic dose range these drugs act primarily as anti adrenergic agents In high dosages some of the compounds (acebutolol alprenolol oxprenolol propranolol) have membrane stabilizing or quinidine like properties in addition to their beta adrenoceptor blocking effects Initially this property was thought to explain the anti arrhythmic potency of beta blockers however it is not an important action with usual doses[4]

Some beta adrenoceptor blocking compounds have partial agonist or intrinsic sympathomimetic properties (acebutolol alprenolol oxprenolol pindolol and practolol) These agents cause a small agonist effect indicating that they stimulate as well as block the receptor This action is dose related increasing in importance with larger plasma concentrations of drug

Some compounds are cardioselective (acebutolol atenolol metoprolol practolol)—that is they antagonize beta receptors in the heart at lower doses than are required for other tissues[4] This property is also dose related becoming less important with increasing plasma concentrations of drug

Beta adrenoceptor blocking drugs also vary in lipid solubility metabolic and excretory pathways and protein binding

Acute toxicity in man Beta blocking compounds are all rapidly absorbed from the gastrointestinal tract The first critical signs of overdosage can appear 20 minutes after ingestion but are more commonly seen within 1 to 2 hours The half life of these compounds is usually short ranging from 2 to 12 hours (Table II) However a depressed cardiac output which reduces both liver and kidney perfusion can significantly increase the plasma half life[34] This might explain the prolonged therapeutic efforts (greater than 12 hours) required in some patients with massive overdosage where cardiac function is compromised In most reported instances of oxprenolol and propranolol self poisoning there was a marked slowing in sinus heart rate with hypotension and circulatory collapse In contrast the two cases of intoxication with pindolol (partial agonist activity) were associated with hypertension and tachycardia Interestingly intoxications with cardioselective agents (atenolol metoprolol and practolol) were not associated with profound bradycardia Overt pulmonary edema was a rare occurence in beta adrenoceptor self poisoning unless the patient had underlying heart disease[3]

The usual electrocardiographic manifestations of beta adrenoceptor blockade include first degree atrioventricular heart block (prolonged PR interval) and sinus bradycardia With massive intoxications disappearance of P waves asystole and intraventricular conduction defects may be seen[5] An intraventricular conduction defect was seen in three of four patients treated for propranolol intoxication at our institution The presence of the intraventricular conduction correlated temporally with the presence of high concentrations of propranolol in the plasma The electrocardiogram normalized as the plasma level fell into the therapeutic range The widening of the QRS complex may be related to the membrane depressant or quinidine effect of propranolol which can manifest itself with high doses of the drug[4] An intraventricular conduction defect has been seen in self poisoning with other beta blocking agents having membrane depressant activity[3] and is rarely described in massive intoxications with agents lacking this property

Bronchospasm is a well known adverse effect in patients treated with beta adrenoceptor blocking drugs and is more frequent with non cardioselective agents[5] It is a rare complication of beta blocker therapy or overdosage except in patients who already have bronchospastic disease Respiratory arrest has also been described with beta blocker intoxication especially with propranolol and has been felt to be secondary to a central drug effect[6, 11]

Propranolol interferes with the glycogen

mobilizing effects of catecholamines [3, 5] Hypoglycemia has been described in patients treated with both insulin and propranolol [3] However hypoglycemia has not been a prominent feature of beta blocker self poisoning alone [3] There has only been one report of hypoglycemia in two non diabetic children who ingested 150 mg of propranolol

Changes in mental and neurological status have been reported in patients treated with propranolol [16, 3] The drug is extremely lipid soluble and readily crosses the blood brain barrier to concentrate in brain tissue Changes in neurological and mental status are less of a problem in drugs which are not as lipid soluble [3] Loss of consciousness has been described as a consequence of low cardiac output in patients treated with beta adrenoceptor blocking agents However changes in mental status and even coma have been seen without evidence of cardiovascular compromise in patients with propranolol self poisoning Convulsions have also been seen in patients with beta adrenoceptor blocker overdosage The seizure activity has been a feature of self poisoning with agents having both high lipophilicity and membrane depressant activity Seizures are not a feature of beta blocker overdosage with agents lacking this membrane depressant effect The convulsions seen with propranolol may be caused by a mechanism similar to that seen with intravenous lidocaine a local anesthetic drug with membrane depressant properties

Plasma drug levels Beta adrenoceptor intoxication may be difficult to recognize especially when the drug is taken in combination with other drugs Although plasma drug levels are available they do not always reflect the degree of beta adrenoceptor blocker intoxication Patients have different degrees of sympathetic tone and different metabolic characteristics so that a specific blood level may produce different clinical signs in each patients Moreover certain compounds (alprenolol propranolol) yield active metabolites which are not detected in the plasma assay It is also well known that the beta adrenoceptor blocking effect appears to last far longer than the short plasma half life would suggest It is therefore important that the physician recognize the clinical manifestations of beta adrenoceptor blocker intoxication and not rely on plasma drug levels Estimating the plasma concentrations of beta blocking drugs may confirm the self poisoning but this is of limited value in the immediate management of patients

Therapy In most cases of beta adrenoceptor blocker self poisoning medical treatment has been successful The majority of reported fatalities occurred in patients who never received medical attention

All beta adrenoceptor blocker intoxications can be treated in a similar fashion The major goals of treatment are (1) to quickly remove any ingested tablets (2) to counteract life threatening cardiovascular and pulmonary effects and (3) to treat central nervous system disturbances

General measures Optimum management of these patients requires intensive supportive care with facilities for continuous cardiac monitoring and ventilatory support Because the effects of beta blocking drugs on the body last longer than their chemical half life in the plasma intensive care may have to be continued for several days [6] The clinical manifestations of intoxication may occur as early as 20 minutes after ingestion of drug but are usually seen one to two hours later [35] Sudden rapid deterioration with cardiovascular collapse is common [3]

Removal of drug Gastric lavage and emesis may allow the tablets to be identified However these measures are unlikely to be sufficient in preventing serious poisoning unless performed early since beta blocking drugs are absorbed rapidly If the ingestion is recent emesis should be initiated unless the patient is comatose convulsing or has lost the gag reflex When these contraindications are present endotracheal intubation should be performed followed by gastric lavage with a large bore tube Activated charcoal five to 10 times the estimated ingested dose or 30 to 50 gm can be given orally or by lavage Sodium or magnesium sulfate 250 mg/kg can be given orally as a cathartic

Hemodialysis is unlikely to rid the body of propranolol since the drug is greater than 95% protein bound This measure has not been tried in gross overdosage however It may be possible to dialyze beta blocking drugs which are more water soluble and less protein bound than propranolol but the value of this procedure has not been assessed

Bradycardia and hypotension Hypotension may be caused by bradycardia depression of myocardial contractility or a central nervous system effect

Patients should be monitored carefully for atrioventricular conduction defects and bradycardia Should these occur doses of atropine at 0.5 to 3.0 mg intravenously in adults[3] or 50 mg/kg intravenously in children should be given to reduce unopposed vagal activity If this is unsuccessful isoproterenol infusion 4 µg/minute may be useful although occasionally larger infusions have been required to completely overcome beta adrenoceptor blockade In one recent report a total of 115 mg of isoproterenol were infused over 65 hours[7] The isoproterenol dose should be monitored according to the response of the pulse and blood pressure Hypotension may be aggravated by the peripheral vasodilatory effects of isoproterenol in which case treatment with dobutamine a cardioselective beta adrenoceptor agonist may be substituted With severe hypotension treatment with alpha vasoconstrictors such as norepinephrine and dopamine may be necessary Glucagon which increases heart rate and improves atrioventricular conduction by non adrenergic mechanisms (not influenced by beta adrenoceptor blockade) may be useful in patients unresponsive to isoproterenol[11] Glucagon is administered as an initial intravenous bolus of 50 µg/kg infused over 1 minute followed by an intravenous infusion of 1 to 5 mg/hour it may be used in conjunction with isoproterenol or dobutamine A temporary transvenous pacemaker should be inserted if heart block or severe bradycardia cannot be readily controlled by pharmacological means

In addition to its electrophysiologic effects glucagon activates adenyl cyclase and enhances myocardial contractility by mechanisms different from catecholamines its inotropic effect is not blocked by beta blockers It is felt to be the initial drug of choice for myocardial depression and hypotension in beta blocker self poisoning although both epinephrine and norepinephrine have been proven efficacious

Pulmonary The physician should rapidly establish effective respiratory function in patients creating an artificial airway if necessary An adequate tidal volume should be maintained Severe bronchoconstriction although rare in self poisoning may require isoproterenol inhalation in larger than usual doses Aminophylline can be given as an initial 5 6 mg kg intravenous bolus over 15 to 20 minutes followed by a continuous infusion of 0 9 mg/kg h r Serum aminophylline levels should be maintained at 10 to 20 µg/ml A beta$_2$ adrenoceptor stimulating drug can also be administered (e g terbutaline)

Hypoglycemia Hypoglycemia is a rare complication of beta adrenoceptor blocker self poisoning This complication if present can be treated with glucose and/or glucagon

Seizures Seizure activity can be seen in beta adrenoceptor blocker overdosage secondary to hypotension hypoxia or hypoglycemia and all these conditions should be corrected Some beta blockers have central nervous system depressant actions and may also cause seizures Intravenous valium has proven effective in controlling seizure activity in several patients

Beta blocker withdrawal Most patients who are successfully treated for self poisoning will have no late sequelae However certain patients following treatment of intoxication may become prone to beta adrenoceptor withdrawal effects[11] (aggravation of chest pain or myocardial infarction in patients with angina pectoris) and should be closely observed for this complication

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Of paroxysmal nocturnal dyspnea

In the wee hours of the morning the patient with left ventricular congestive heart failure is suddenly awakened from his sleep with an acute onset of suffocation and dyspnea—a frightening experience for him He suddenly and properly rises from his bed and walks in search of fresh air and stands by an open window Within a few minutes he feels fine Why? His clinical state improves in large part because of the assistance of the force of gravity a force exploited by evolutionary processes and physiologic development Upon standing a part of the blood pumped from the lungs by the left ventricle to the legs and feet and areas of the body below the heart remains in the systemic veins located below the heart This shifts blood away from the congested pulmonary circulation relieving the lungs of the excess engorging blood which through respiratory reflexes (Hering Breuer etc) causes the respiratory discomfort (suffocation and dyspnea) and the patient then feels better This special form of hemometakinesia provides comfort for the patient Other readjusting physiologic factors are probably involved but they are probably of less importance

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Stability of permanently implanted endocardial electrodes during open heart surgery

Much has been written about the stability of transvenous electrodes during the first few weeks of implantation but little is known about long term anatomical stability when these electrodes are subjected to vigorous surgical manipulation It has been shown that ventricular electrodes become encapsulated in a fibrous sheath which presumably holds them securely in position and in fact makes extraction difficult at times Nevertheless the stability under unusual circumstances has not been demonstrated up to now

We have had the opportunity to observe electrode stability in 15 open heart operations on 14 patients over the past six years Nine of the 15 procedures were aortocoronary bypasses three of them combined with valve replacements or ventricular aneurysm resection There were two aortic valve replacements one repair of a paravalvular leak and three cases of surgical ligation of the AV node or bundle of Kent The rather complex cardiac surgical procedures in this series reflect the extent of myocardial disease that would be associated with atrioventricular block or complex tachyarrhythmias In one patient it was essential to restore atrioventricular synchrony and therefore an atrial synchronous pacemaker (VAT) was implanted at the time of valve replacement and double bypass In another patient an unexplained rise in pacing threshold was seen a year after surgery and the electrode was replaced it is problematic whether this could have been related to subtle movement of the electrode at the time of the open heart procedure

Of the 14 electrodes eight were [illegible] models with a small silicone rubber shoulder near the tip four were bipolar Medtronic electrodes (Model 6901) and [illegible] were small Cordis thumb tack" (or ball tip) electrodes The electrodes had been in place for 2 to 52 months with an average of 18 8 months During the operation the implanted pacemaker was managed in a variety of ways Usually its presence was ignored However when the firing of the pacemaker became troublesome the pulse generator output was suppressed by external overdrive with an external pacemaker whose pacing electrodes were placed on the skin over the implant In two instances the pacing mode was converted to fixed rate by application of a sterile magnet In one case the pulse generator was temporarily explanted

In the course of these operations the heart was usually manipulated rather vigorously particularly during coronary bypass surgery where anastomoses to obtuse marginal vessels required elevation and rotation of the heart to a rather extreme degree Most patients also had apical ventricular sump drains which required further manipulation of the apex Despite this there were no electrode dislodgements and in all cases satisfactory pacing continued postoperatively These results suggest that permanently implanted transvenous electrodes are securely positioned in the heart probably by virtue of the fibrous sheath that forms around the tip and that this fixation is secure enough to withstand the manipulation of the heart during open heart surgery

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Seating as a variable in clinical blood pressure measurement

The assessment and management of hypertension in clinical practice is based on the measurement of the so-called casual blood pressure. Because of the physiological variability of blood pressure, care is required to standardize such factors as posture and time of day on each occasion the measurement is repeated.

During research into the treatment of hypertension by behavioral techniques, systematic differences were observed between blood pressures measured sequentially by a physician and by a psychologist. This was initially accepted as the response of patient to examination by a physician, a circumstance known to elevate blood pressure, at least in the short term. A systematic difference due to the use of an ultrasonic technique (Arteriosonde 1216) by the psychologist and by the use of the auscultatory method by the physician was excluded by simultaneous measurements with a common arm cuff. An alternative hypothesis was formulated that the difference in blood pressure measurements was due to a difference in seating and resultant postural tension.

An initial experiment was undertaken by non-medical personnel in order to eliminate any response caused by a physician. Twenty-one treated male hypertensive patients aged between 25 and 65 years were examined. Blood pressures were simultaneously measured in the right arm after five minutes of quiet sitting, taking the mean of three readings. Measurements were taken using the auscultatory technique (muffling taken as diastolic) and by an ultrasonic method (Arteriosonde 1216); both instruments were connected to a common cuff. Patients were examined seated upright in a recliner chair and seated upright on an examining table sequentially in counter-balanced order. The right arm was supported, palm up, at heart level to obviate a potential source of error.

Significantly lower systolic and diastolic blood pressures were observed with patients seated in the recliner chair compared to those obtained while they were seated on an examining table (Table I). In individual cases the differences were marked, the greatest being 25 mm Hg systolic and 18 mm Hg diastolic. Again no significant differences were found between simultaneous observations made by the auscultatory and ultrasonic methods. Examination of another 11 subjects showed that the reduction of muscular effort by support of the dangling feet of patients seated on the examining table did not abolish the difference in readings between the two conditions.

A further experiment was undertaken to compare the readings obtained when a patient was seated upright in a recliner chair in contrast to the readings found with the patient seated in an office chair. It was proposed that the muscular tension in the office chair with some back support might be intermediate between that experienced while seated on the examining table and that found seated in the recliner chair and hence that blood pressure differences would be correspondingly reduced. Again the right arm was supported while blood pressures were measured simultaneously by the auscultatory and ultrasonic techniques. In this experiment the differences in systolic blood pressure were not so marked (Table II) but the differences for diastolic blood pressure remained high. The reduction in muscle tension provided by back support in an office chair may have reduced the systolic blood pressure difference.

Table I Auscultatory and ultrasonic blood pressure measurements taken seated upright in a recliner chair and upon an examining table (N = 21; mm Hg; Mean ± SD)

	Chair	*Table*	*p*
Systolic auscultatory	131.5 ± 21.0	139.0 ± 20.7	<0.001
ultrasonic	133.8 ± 20.9	140.0 ± 20.9	<0.001
Diastolic auscultatory	83.7 ± 10.8	93.7 ± 11.1	<0.001
ultrasonic	81.6 ± 10.4	93.8 ± 12.2	<0.001

Table II *Auscultatory and ultrasonic blood pressure measurements taken seated upright in a recliner chair and in an office chair (N = 19; mm Hg; Mean ± SD)*

	Recliner chair	*Office chair*	*p*
Systolic auscultatory	136.9 ± 18.5	139.5 ± 16.2	>0.10
ultrasonic	132.4 ± 19.9	140.0 ± 16.5	<0.01
Diastolic auscultatory	89.6 ± 8.2	96.5 ± 6.5	<0.001
ultrasonic	88.2 ± 10.3	96.4 ± 9.0	<0.001

Postural muscular tension seems to be a likely explanation for the findings in these studies. A similar explanation may also account for the findings of Schneider and colleagues, who found higher examining table than recliner chair blood pressure readings. They postulated the difference being due to an effect of measurement by a physician. In the present study the differences remained when no physician was involved in measurement.

These findings are of importance in investigational studies involving measurement of blood pressure. For comparable results measurements must be taken under the same conditions of upright seating. This particularly applies in experimental studies of behavioral therapy where treatments are carried out in a recliner chair. Again, similar considerations apply when decisions are made regarding alteration of pharmacological therapy based on serial blood pressure measurements.

The good agreement of the auscultatory and ultrasonic techniques of blood pressure measurement found in the present study is evidence for the validity of the ultrasonic method used here.

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Finally these findings suggest that further investigation would allow more precise definition of the variables inherent in the term casual as applied to blood pressure measurement

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Hair dye genotoxicity

Misuse of domestic substances drugs in particular is known to cause cardiovascular disease Pulmonary hypertension and cor pulmonale result from intravenous injection of tablet (oral) forms of drugs where the filler talc (magnesium trisilicate) causes a granulomatous reaction in the pulmonary vessels Talc has also been reported to cause calcification of the pericardium

Cosmetics may also cause heart disease and Kamm reported the death of a boy due to ventricular fibrillation following inhalation of Arrid Extra Dry aerosol deodorant Here it was implied that the volatile hydrocarbons caused cardiac arrhythmias but such compounds may be more generally toxic to connective tissues as indicated by Findlay and associates in their report of ochronosis and colloid milium in negroes following the use of strong bleaching creams containing volatile hydrocarbons

Of interest to this area of study may be the results my colleagues and I published recently on chromosomal damage and hair dyes Various hair dye ingredients have been shown to be mutagenic and are now being shown to be carcinogenic in laboratory animals We had also shown that hair dye ingredients could cause toxicity and chromosomal damage to mammalian cells *in vitro*

The purpose of our most recent study was therefore to look for chromosome damage in the lymphocytes of people exposed to hair dyes For this we had 60 professional hair colorists from London salons and 36 age and sex matched controls All blood samples were coded and were analyzed blind

When levels of chromosome damage of various types were compared in professional hair colorists and controls there was no difference This is probably because many colorists wear gloves for handling semi permanent and permanent dyes and also due to the horny protective layer of the hands and the lack of sebaceous glands (the most likely route of absorption)

The questionnaires completed by our volunteers were so detailed that we were also able to compare those men and women whose own hair was dyed with those who never dyed their hair The findings were interesting Women who dyed their hair had significantly more lymphocytic chromosomal damage than women of the same age and habits who did not This is probably due to facilitated absorption via the vast numbers of sebaceous glands in the scalp

In men the findings were a little confusing in that men with undyed hair had significantly more damage than men with dyed hair However they were on average 10 years older and age related increases in lymphocytic chromosomal damage have been reported Furthermore the men dyed their hair much less than the women

These results suggested to us that hair dyes were penetrating the scalp and causing untoward genotoxic effects in the lymphocytes Whether any other tissues are affected in a similar way we do not know but these kind of findings suggest that to educate people to exercise proper health habits and to use potentially hazardous cosmetics with moderation (if at all) may alleviate much suffering

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Mitral valve prolapse—systolic click murmur syndrome

To the Editor

In their informative editorial entitled "Mitral valve prolapse: the specific billowing mitral leaflet syndrome or an insignificant non-ejection systolic click" (AMERICAN HEART JOURNAL 97:277, 1979) Doctors Barlow and Pocock mention that they postulated, as later did Wooley, that many cases of so-called DaCosta's syndrome or neurocirculatory asthenia (NCA) are examples of the billowing mitral leaflet syndrome.

I should like, however, to point out that we have made the same observation independently in an article submitted to the same journal towards the end of 1974. We then noted: "the striking similarity between the symptomatology and ECG findings in systolic click murmur syndrome (SCMS) and cases of NCA leads to doubt whether many cases of so-called NCA are not in fact suffering from the SCMS." Furthermore we stressed that "all cases labeled as NCA should, in our opinion, be reviewed and carefully ausculated in different postures in order to exclude SCMS."

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Hemodynamics for hematologists

To the Editor

I wish to offer a bit of constructive criticism of the recent excellent review of coagulation and antithrombotic therapy by Wessler and Gitel. They write (page 815) that ". . . dextran increases the rate of blood flow which may particularly in cardiac patients precipitate pulmonary edema." It is true that if all other factors are unchanged, dextran could be expected to increase flow as a result of the reduction in whole blood viscosity

$$(F = \frac{\Delta P \times R^4 \pi}{8L \times \eta})$$

which results from hemodilution and perhaps via other mechanisms. However, the increase in flow which occurs is not the cause of the pulmonary edema which is sometimes seen during therapy with dextran.

Pulmonary edema results either from changes in the balance of opposing forces in pulmonary capillaries, capillary hydrostatic pressure and plasma oncotic pressure, or by changes in the permeability of the pulmonary capillary membrane. Dextran usually produces pulmonary edema by increasing the pulmonary capillary hydrostatic pressure as a result of expansion of intravascular volume which raises left ventricular filling pressure, particularly in patients with an abnormal left ventricle which cannot respond appropriately to the increased volume. There is one report of a case in which pulmonary edema was alleged to have occurred as a result of damage to the pulmonary capillary membrane, but the purported mechanism in that case is suspect as relevant intravascular pressures (left ventricular end-diastolic, left atrial or pulmonary capillary) were not measured.

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Reply

To the Editor

We should like to thank Dr Prescott for his clearer exposition of the mechanisms whereby dextran may precipitate pulmonary edema.

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Effects of verapamil on ventricular premature beats of acute myocardial infarction

To the Editor

Many years ago it was shown that verapamil in open-chest dogs is extremely effective in prevention of ventricular fibrillation induced by ligation of the left descending coronary artery. Kaumann and Aramendia observed that only one out of 10 animals pretreated with the drug fibrillated while this

evidence occurred in 10 out of 11 controls This observation wa overlooked till recently when the results of Kaumann and Aramendia were confirmed by Fondacaro Han and Yoon They found that verapamil is also extremely effective in abolishing rapidly repetitive beats induced by acute coronary occlusion

These experimental data led u to verify the usefulness of the drug in the management of ventricular premature beats (VPB) occurring in human myocardial infarction

Patients methods and results

Twenty-eight patients with myocardial infarction who presented frequent VPBs in the first 48 hours of their illness were included in the study The selection criteria were frequency of VPB (more than 10/minute) absence of heart failure absence of hypotension (blood pressure less than 100 mm Hg) and absence of bradycardia (heart rate less than 60/minute) Eighteen patients had uniform and 10 had multiform VPBs I aired extrasystoles were present in two patients with uniform VPB and in two with multiform VPBs R-on T phenomenon was observed in one patient with uniform and in five patients with multiform VPB

Verapamil was administered intravenously in a single dose of 0 10 mg/Kg injected in 2 minutes under continuous ECG recording Moreover blood pressure was checked every 60 second for 5 minutes after drug administration

In 24 patients VPB disappeared in an interval of time varying from 1.30 to 3 minutes Only in two of these patients were there relapses of the arrhythmia durin the 3 hours following administration of verapamil in one patient the relapse occurred after 15 minutes and in the other one after 70 minutes In four cases VPBs persisted in all these cases VPBs were isolated without R on T phenomenon In the first 5 minutes after dru injection none of the patients (all in sinus rhythm) pre ented changes in heart rate greater than 10/ minute compared to the heart rate before the administration of verapamil Following this initial period a reduction of heart rate was common but in none of the patients did the heart rate reach values lower than 56/minute Undesired side effects did not occur but in almost all patients a transient and mild redu tion of blood pressure (not greater than 20 mm Hg) o urred

D scuss on

The effectiveness of verapamil in VPBs of acute myocardial infarction (abolition of arrhythmia in 85% of our cases) raises interesting questions about the mechanism of the antiar rhythmic activity of the drug in this kind of arrhythmia Although the understanding of the mechanism of antiarrhyth mic drugs in clinical practice is generally hampered by the absence of suitable experimental model of arrhythmias and obviously this is true also for myocardial infarction it is pos ible to advance some hypotheses

Arrhythmias in myocardial infarction may be caused by slow conduction with reentry and by abnormal automatic activity Electrophysiological recordings from experimentally infarcted tissues have shown bioelectrical changes potentially responsible for these mechanisms namely action potentials with slowed depolarization rate and rhythmic automatic depolarization both arising from low transmembrane resting potential Many experimental studies have been carried out in order to elucidate the electrophysiological characteristics of both these electrophy iological phenomena It has been shown that the loss of resting potential in myocardial fibers in the range between −90 and −60 mV is associated with a decrease in availability of the fast sodium channels responsible for the normal depolarization phase and thus is associated with the appearance of depressed fast responses" with a slower conduction velocity Following the depolarization at mem brane potential levels (−50 mV or less) at which the fast sodium channels are completely inactivated the excitability of the fibers can be still maintained by the appearance of "slow responses" i.e., slowly propagated action potentials with a low depolarization rate due to depolarizing currents flowing through slow channels That slow responses can be responsible for slow conduction unidirectional block and reentry in relatively short loops of Purkinje fibers has been demonstrated by careful electrophysiological studies

Evidence for the presence of true "slow responses" has not been directly obtained in infarcted myocardial tissues, but is presently restricted to in vitro fibers exposed to beta adrener gic stimulating amines in the presence of high extracellular potassium concentrations however it may be noted that both these conditions are considered as particularly probable in infarcted tissues in vivo In particular the accumulation of extracellular potassium may reach significant values in infarcted tissues since the loss of intracellular potassium is associated with a reduction in exchange between the intersti tial and the vascular paces

With regard to the role of abnormal automatic activity in the induction of arrhythmias in myocardial infarction much attention has been devoted in the last years to the rhythmic automatic depolarizations (oscillatory activity su tained rhythmic activity) which has been hown to occur in ventric ular or Purkinje fibers following many experimental interven tion able to induce a membrane depolarization Such an abnormal activity may be induced at the border of the ischemic zone by short circuit depolarizing currents produced by the contact between normal and depolarized tissues. Experimental evidence indicates that the oscillatory activity is chiefly due to an increase in the slow inward current coupled with a decrease of a time-dependent outward potassium current

Verapamil is a powerful inhibitor of the slow inward current in myocardial cells although the action of the drug in this respect is not strictly specific since other ionic currents seem to be affected According to its main electrophysiological action it has been shown that verapamil is highly effective in suppressing either the slow responses or the oscillatory poten tials in cardiac muscle in vitro Therefore indirect evidence suggests that the clinical effectiveness of verapamil in arrhythmias of the early phase of myocardial infarction is chiefly due to its peculiar electrophysiological effect since the drug has been shown able to antagonize bioelectrical phenom ena potentially responsible for both low conduction with reentry and increased automaticity in infarcted tissues

Finally it may be pointed out that this interpretation is not necessarily opposed to the observation that verapamil is able to reduce the extent of ischemia induced conduction delay within the ischemic zone in dog heart In fact the improve ment of conduction as recorded from epicardial electrograms, may be interpreted as a consequence of a verapamil induced block of slow responses responsible for slow conduction and reentry and of the consequent unmasking and recruiting of depressed fast responses and/or normal fast responses in less damaged or undamaged fibers. This hypothesis may also

account for the reduced fractionation of the epicardial electrogram recorded under verapamil from the ischemic zone which has been observed in the above-mentioned experiments

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Book reviews

Noninvasive Diagnostic Techniques in Vascular Disease Edited by Eugene F Bernstein M D Ph D St Louis 19"8 The C V Mosby Company 437 pages Price $4 50

This publication is welcomed The peripheral vascular diseases have received little attention recently even though they remain important and common diseases of man The pathophysiology of diseases of the extremities is not particularly different from that of the viscera such as the heart This book with many contributors reviews the numerous methods used to study the state of the peripheral circulation—e g radionuclides, plethysmography pulse echo-ultrasonography pressure recording phonocardiography Doppler recording etc But the importance of environmental temperature and relative humidity of the examining room position of the part under study the history and physical examination of the *patient s state of health and the diseases etc* are not clearly defined The extent of evaluation of the patient s illness can be impressively determined with accuracy in the examining rooms and at the bedside without expensive gad etry Furthermore even properly employed complex apparatus can be expensive and misleading Nevertheless this book defines the present state of practice and thinking in some clinical centers. This is a very useful book and a good beginning in the understanding of and the use of methods and technics as employed today There is no substitute for a thorough knowledge of circulatory physiology clinical medicine and experience Complex methods of study must be introduced not routinely but when definitely indicated

Molecular and Cellular Aspects of Vascular Smooth Muscle in Health and Disease Edited by D F Bohr and F Takenaka Published in Blood Vessels Vol 15 No 1 3 Basel 19"8 S Karger 216 pages Price $47 50

This issue of *Blood Vessels* contains the papers presented at a symposium held in January 1977 in Honolulu on the molecular and cellular aspects of vascular smooth muscle in health and disease This issue is extremely important The range of subjects discussed is wide and interesting Vascular physiology and diseases unfortunately are neglected in medical education and practice This symposium *reflects very* effectively the importance of the smooth muscle of blood vessel This is a very good publication which is worthy of study by all physicians and housestaff The issue is certainly worth owning

L Echocardiographie en Pratique Clinique By G Drobinski, P Botreau Rouseel and Y Grosgogeat Paris 19 8 Masson et Cie 110 pages

This is a small practical clinical discussion of echocardiography (ECHO) in French and published in a pocket size paperback The book is another of many others already published in English on the subject The book includes discussions of history principles of ECHO the normal ECHO mitral and aortic valve disease diseases of the tricuspid and pulmonary valves congenital heart disease left ventricular *disease coronary artery disease pericardial disease and artificial* valves. The book is concisely written reliable and well organized The illustrations are very good and the book is very useful and concise

Venous Problems Edited by John J Bergan and James S T Yao Chicago 19/8 Year Book Medical Publishers Inc 613 pages Price $42.50

This symposium on venous problems is dedicated to Dr Geza deTakats, an outstanding vascular surgeon and a gentleman of absolute integrity The contributors are numerous The approach is primarily surgical This book like many publications in the medical literature fails to distinguish conservative from radical or conservative from medical management The authors fail to realize that both medical and surgical management can be radical or conservative The book is divided into many sections basic physiology of the venous circulation chronic venous insufficiency diagnosis of venous thrombosis thromboembolic disease post phlebitis syndrome and prevention of thromboembolism The discussions are interesting and the presentations are rather complete This is an excellent review of venous diseases, especially of venous thrombosis and thromboembolic disease The illustrations are good and the publishers have done an excellent job in printing and binding Dr Geza deTakats *should be proud of this book dedicated to him*

Books received

Fonomecanocardiografia Clinica By Bernardo L Fishleder and Ignacio Chavez Mexico City 19"8 La Prensa Medica Mexicana 1 098 pages

Biophysical Aspects of Cardiac Muscle Edited by Martin Morad New York 19"8 Academic Press Inc 406 pages Price $19 50

Angina Pectoris By Ekkehard Gill Stuttgart 19"8 Gustav Fischer Verlag 610 pages

Radiology of the Heart and Great Vessels th d edition By Robert N Cooley M D and Melvin H Schreiber M D Baltimore 19 8 The Williams & Wilkins Company f 3 pages Price $65 00

Bing Award

The 1980 Richard Bing Award of the International Society for Heart Research will be given to a young investigator (35 years or less) in the field of heart research at the Tenth Heart Congress Moscow USSR September 23 28 1980 Inquiries should be addressed to Dr N S Dhalla Secretary General of ISHR Faculty of Medicine University of Manitoba Winnipeg Canada R3E 0W3

AHA postgraduate courses

The American Heart Association announces the following postgraduate courses Council on Circulation Scientific Session February 1? 15 1980 Keystone Colorado Robert Zelis M D Course Director Eleventh Annual Nephrology Conference February 25-26 1980 San Antonio Texas Jay H Stein M D and H John Reineck M D Course Directors Address inquiries to Administrator Postgraduate Programs American Heart Association 7320 Greenville Ave Dallas Texas 75231 Telephone (214) 750-5441

Cardiopulmonary Nuclear Medicine 1980

The conference on Cardiopulmonary Nuclear Medicine will be held February 14 16 1980 at the Turner Auditorium The John Hopkins Medical Institutions Baltimore Maryland Twenty hours AMA Category I credit Fee $150 Contact Program Coordinator Turner 22 720 Rutland Ave Baltimore Md 21205 Telephone (301) 955-5880

Contemporary Management of Stroke and Coronary Disease

A medical symposium entitled Contemporary Management of Stroke and Coronary Disease will be held February ? to March 1 1980 in Taos New Mexico For further information contact W J Levy M D Symposia de Santa Fe PO Box 5175 Santa Fe N M 87502

Second Pan American Congress on Diseases of the Chest

The Second Pan American Congress on Diseases of the Chest will be held April 19 ?3 1980 in Rio de Janeiro Brazil The Brazilian Chapter of the International Academy of Chest Physicians and Surgeons, an affiliate of the American College of Chest Physicians, will be the host For further information write Jesse P Teixeira M D Second Pan American Congress on Diseases of the Chest Caixa Postal 3?0 Rio de Janeiro RJ 20000 Brazil

North American Society for Cardiac Radiology

The annual meeting of the North American Society for Cardiac Radiology will be held April 23-?9 1980 in San Francisco California at the Mark Hopkins Hotel

Eighth Annual Intensive Care Symposium

The Eighth Annual Intensive Care Symposium will be held April 25-28 1980 at the Eden Roc Hotel Miami Beach Fla The symposium will be sponsored by the University of Miami School of Medicine Division of Surgical Intensive Care Course hours 21 AMA Category 1 For further information contact Division of Continuing Medical Education D?3-3 University of Miami School of Medicine PO Box 016960 Miami Fla 33101 Telephone (305) 547 6?16

Joint Meeting of International Society of Hematology and International Society of Blood Transfusion

The Joint Meeting of the Eighteenth Congress of the International Society of Hematology and the Sixteenth Congress of the International Society of Blood Transfusion is scheduled for August 16-2? 1980 in Montreal Canada Inquiries should be addressed to ISH/ISBT Congress—Montreal ??2 Sherbrooke St West Montreal Quebec Canada H3A 1G1 Telephone (514) 392 6?44 or Telex 05-268510

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